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Afferent Nerve Activity in Thoracic Cardiac Nerves

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AFFERENT NERVE ACTIVITY IN THORACIC CARDIAC NERVES

by

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BIOGRAPHY

John Andrew Armour, born May 22, 1937, in Montreal, Quebec, Canada, was educated at Sedbergh School, Montebello and received a B.Sc. degree at McGill University in 1958 and an M.D. degree from the University of Western Ontario in 1963. After internship and two years of cardiovascular surgical residency, he spent a year at the University of Alabama with Dr. D.A. McDonald before coming to the Department of Physiology of Loyola University. Since 1968, under the guidance of Dr. W.C. Randall, he worked with Drs. John Pace, Jim Wechsler, Jack Goldberg, Peter Geis, and Messrs. Dave Lippincott and Gil Hageman, as well as with Drs. Bob Wurster and Messr. Bob Foreman. The author is a member of the Society of the Sigma Xi and an associate member of the American Physiological Society.

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This work has evolved and been nurtured under the tutelage of the author's advisor, Dr. Walter C. Randall; without his honest involvement this work would never have been possible - the best method of teaching is by example. The constant advice and encouragement of Dr. Robert D. Wurster are also gratefully acknowledged, for without his expertise this study could not have been initiated. Grateful acknowledgement is proffered to Ms. Carol Ofenloch for her organization and typing of the thesis, and to Ms. Mira Milosavljevic for the histological preparations.

TABLE OF CONTENTS

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF FIGURES

LIST OF TABLES

CHAPTER I

STATEMENT OF THE PROBLEM

Concepts of cardiac function have been dominated by the thesis originated by Frank (128) that on a beat to beat basis a larger ventricular diastolic volume causes the subsequent systolic pressure to increase above control levels. The extension of the end-diastolic volume - peak systolic pressure relationships to include mammalian hearts (99, 127) has proved to be the predominant concept explaining cardiac function over the past fifty years. Although much cardiovascular investigation has continued apace, the concept of heterometric autoregulation still prevails, with modification to include "extra-cardiac" controls such as homeometric autoregulation (117). The role of the efferent autonomic nervous system in cardiac function, generally considered a minimal part of the homeometric mechanisms (117), has only recently been emphasized (106) even though before the turn of the century concepts of heart failure were dominated by

neural theories (40).

Elucidation of the efferent control of the parasympathetic and sympathetic branches of the autonomic nervous system (106) upon cardiac behavior has demonstrated their discrete functional roles. Despite many attempts to analyse cardiac receptors (95), only atrial receptors have been clearly demonstrated to function physiologically; in contrast ventricular receptors have been demonstrated only during unphysiological states (94, 118) and thus their role has been questioned and neglected. It was considered important first of all therefore to determine the presence of physiologically-active cardiac and, in particular, ventricular receptors; secondly to determine if all cardiac receptors have afferent projections which would demonstrate the anatomic consistency and localization that the comparable efferent cardiac nerves are known to possess (106). The demonstration of afferent and efferent cardiac neural mechanisms which are highly localized and specific might account for neuronal mechanisms controlling regional cardiac dynamics.

It is the purpose of this dissertation: 1) to evaluate the function and location of all the cardiac receptors and, 2) to deliniate the specific anatomic pathways of the receptor afferents. These findings will be discussed in

relationship to their role in cardio - cardiac regulating reflexes.

CHAPTER II

LITERATURE REVIEW

A. Concepts of Cardiac Function

William Harvey initiated the concepts concerning functioning of the heart which prevail today (129); by direct visual observations he dispelled centuries of confusion and elucidated the circular motion of blood as well as the pumping action of the heart. In his second major treatise, "Anatomical Exercises on the Generation of Animals" (129), availing himself of the most unusual case of the son of Viscount Montgomery, he concluded that the heart lacked sensory mechanisms and therefore was not under the control of the "will." This view was altered, so that by the turn of the last century Austin Flint (40) voiced a consensus of opinion by stating that while the heart was a muscular organ, the nervous system was important in regulating the frequency and force of muscular contractions. Present concepts of cardiac function are dominated by work performed soon after the turn of the century which

developed the thesis that the initial length of the cardiac fibers during diastole primarily determines the output of the organ (99, 110, 127). This behavior of mammalian cardiac muscle was first noted with skeletal muscle as well as the reptilian heart (13) and has also been demonstrated in segments of intact (48, 110) as well as isolated hearts (72). It is known that under in vitro circumstances the myocardial sarcomeres do not contract uniformly (56), but rather contract to varying degrees during systole; thus it is difficult to be simplistic about contractile processes. The length - tension relationships operating in the in situ heart (heterometric autoregulation) are effected by additional extracardiac factors from without the heart (homeometric autoregulation) particularly the neuro-chemical milieu supplied by the autonomic nervous system (117). Thus, while the heart is thought to behave in accordance to the degree of diastolic distention, the circulating humoral agents and autonomic nervous system act as dominant modifying influences. This thesis is exemplified at present by the view that the intact heart responds to stress primarily by alterations in heart rate and not force of contraction (123); this is all the more tenable when one considers that the intact heart is prevented from large end-diastolic volume changes by the almost indistensible

pericardium.

It is noteworthy that Henderson (69) in 1906, while concentrating upon the diastolic phase of the cardiac cycle, concluded that the state of diastolic tone, i.e. the bathmotropic state, was an important determinant of cardiac function and complemented inotropic, dromotropic, and chronotropic conditions which were the other factors considered to be important (12). However, a few years later (50) he repudiated the concept of bathmotropism even though he was able to demonstrate vagally-induced alterations in cardiac tone. The cardiac diastolic state has received scant attention since that time, as has the concept of instantaneous changes in systole. Cardiac contraction is considered to be determined by the initial length of the diastolic myocardium - a concept of length with a fixed "tone" - upon which extracardiac forces interplay. The neural regulation of the heart has therefore not received much attention, with the exception of heart rate control. In the following sections of the Literature Review (1) anatomical and (2) physiological roles for cardiac receptors and the efferent neural regulation of the heart are discussed.

B. Cardiac Receptors

Physiological receptors are defined as those structures which transduce the physical - chemical milieu of

their environments into neuronal activity.

1. Anatomy

There are numerous reports of neural tissue in the atria, ventricles, and great vessels of the heart (116, 120, 121). However, major difficulty arises in the differentiation of afferent from efferent nerves - a task which to date has not been adequately performed due to the fact that the presence of ganglia in the heart (30, 39, 59, 130) allows the possibility of functioning afferent and efferent nerves to remain after thoracic neural ablation or even after cardiac transplantation. Cardiac neural tissue has been documented by light microscopy (16, 25, 53, 59, 60, 62, 81, 87, 90, 120, 130) as well as electron microscopy (44, 53, 85, 121, 131). A number of nerve endings with their associated cardiac tissue processes have been reported using light microscopy, particularly in the Russian literature, as reviewed by Khabarova (59). However, electron microscopy pictures to date have demonstrated only non-myelinated C-fibers (44) with nerve endings approaching to within 200A° (20 nm) of cardiac cells (121). The afferent nerves, which are considered relatively resistant to degeneration in the period following surgical neural ablation (85), have led to their supposed identification often with complex neural - muscular formations. The imaginative speculations concerning

receptors identified by light microscopy as reported by some Russians (59) have been equalled by Western researchers (25); cardiac unencapsulated endings identified as stretch receptors and called "baroreceptors" have been reported (55). Colderidge et al (23) located a few receptor sites via direct probing of the superior vena cava, right atrial and right pulmonary vein, left atrial junctions, and determined histologically that the receptor areas contained branching myelinated fibers forming flattened terminal plates parallel to the endocardial surfaces. Despite the plethora of reports, no definitive proof of specific cardiac receptors has appeared; rather the only convincing reports of cardiac receptors occur in the physiological literature.

2. Physiology

The report by Adrian in 1921 (2) demonstrated that thoracic autonomic nerves contain afferent nerve activity related to the cardiac cycle; physiological evidence thus was obtained for the long postulated receptors arising from the cardiovascular system (52). Ever since Bainbridge (11) in 1915 proposed that distention of the vena cava - right atrial region effected heart rate, investigators have assumed the presence of cardiac receptors, with little or no proof of their existence (13). Nevertheless, as late

as 1946, the functional significance of cardiac receptors was in doubt (128). Activation of cardiac receptors via various means has been demonstrated to effect cardiodynamics. Following the report of Bainbridge, mechanical interventions in various regions of the heart have been performed to determine the presence of cardiac receptors; modification of heart rate, blood pressure, as well as total peripheral vascular resistance have been reported to be effected by such reflexes. Distention of the venoatrial ventricular junctions altered heart rate (33, 54, 68, 86); these effects were abolished by vagotomy. Atrial mechanoreceptors were stimulated by chemicals (54, 86); this knowledge has been employed to investigate neural traffic from cardiovascular receptors sensitive to aconite, veratrine and mistletoe extracts (26, 54). The local distention of varying cardiovascular areas, including the left ventricle (114), caused a decrease of heart rate and total peripheral resistance. Perhaps the best investigation to date in this regard was the demonstration that local stretching of the sinoatrial zone of the right atrium greatly augmented heart rate (21) - an investigation open to question due to the direct effects of nodal stretching which must have occurred. Local myocardial alterations also initiated reflex changes in heart rate and the

vascular system; the afferents were localized in the vagi (86) as well as the third and fourth thoracic rami of the sympathetic nervous system (125). Definitive proof of cardiovascular receptors however had to await the advent of direct nerve recordings to demonstrate receptors in the heart (70, 95).

Action potential recordings from thoracic nerves demonstrated cyclic impulses related to heart rate (2) and paved the way for the demonstration of receptor activity in the carotid sinus nerve from carotid sinus baroreceptors; Bronk and Stella (18) found that between 60 and 140 mm Hg carotid sinus pressure, the carotid sinus nerve activity increased in a nearly linear fashion. Other authors have further elucidated this mechanoreceptor mechanism (61, 63, 64) as well as similar receptors with traffic in the aortic depressor nerve (1); these local stretch receptors are known to be sensitive to length changes as well as the chemical milieu, i.e. norepinephrine concentrations (1). Atrial receptors have also been clearly demonstrated. However, there appears to be a divergence of opinion as to their location and activity. Perhaps this is because most investigators have employed veratrum or other irritating drugs to demonstrate the receptors (27, 31, 93, 118). Atrial receptors were classified as "A" or "B" by Paintal

(93) depending upon their activation time in each cardiac cycle. The "A" type of receptor fired during the "a" wave of the atrial pressure trace, atrial contraction, whilst the "B" type of receptor fired during the "v" wave, or synchronous with atrial distention. Both of these receptors (22, 23, 45, 81, 86) were considered to fire in a fashion which is linear in relation to the atrial volume (31), and have been localized primarily in the posterior atria near the great vessels. These afferent nerves were found to course primarily in the vagi and it is worth emphasizing that chemical stimulation was usually required in order to initiate their firing.

A number of investigators have reported ventricular receptors (24, 94, 118, 119, 122, 126), however with the exception of one report (24) the evidence was not convincing. Once again veratridine or other chemicals as well as mechanical distortion (94, 119) were needed to excite ventricular receptors (14). Ventricular receptors, functioning physiologically, have been divided into two types: one type of receptor fired in relation to the cardiac cycle and had maximal traffic during systole; in contrast the afferent activity of the second type which were located near the epicardium, seemed unrelated to any particular period in the cardiac cycle. Often receptors

have been considered ventricular because they were modified by ascending aorta occlusion; however, aortic occlusion could activate receptors in the root of the aorta and without discrete localization by touch or by noting ectopic beats that fail to open the aortic valves, such reports may be misleading (27, 115). Veratridine, nicotine, and capsacin were employed in these studies to cause receptor activation and this further qualification may in part be responsible for the lack of importance ascribed to cardiac receptors. The cardiac receptors are known to have afferent neurons in both the parasympathetic (24, 81, 107) and the sympathetic (74, 75, 77, 122) nerves of the autonomic nervous system. Mechanoreceptors have been postulated in the pulmonary artery (10) however without adequate proof. In summary, adequately defined ventricular receptors (24) are neither numerous or very dynamically active.

Chemoreceptors in the aorta and carotid regions of the cardiovascular system (29, 37, 88), as well as the coronary artery system (27, 28, 41) have been postulated. To date, the anatomical localization has confirmed the presence of chemosensitive bodies to exist in the carotid body and aortic arch (29); the injections of drugs into the coronary system via local perfusion of the upper septal vessels (61) has strengthened the evidence for cardiac

chemoreceptors and the postulated local liberation of acetylcholine to stimulate the receptors (38). To date there is evidence for chemoreceptors in the major vessels, but their existence in the coronary artery system is speculative.

In summary, there is ample evidence for the existence of cardiac mechanoreceptors - especially those in the atria. Ventricular receptors, although adequately demonstrated in one study (24), have not been accepted as being physiologically important (86); this is perhaps because their physiological activity has not been investigated or because in most instances required unphysiologic means such as the use of drugs for their demonstration. Although chemoreceptors have been demonstrated in the carotid artery and aortic arch, to date they have been only postulated to exist in the heart (41). There is adequate anatomical evidence for cardiac neural elements which can be considered as receptors, but their dynamic behavior and physiological importance are still open to question.

C. Efferent Neural Control of Cardiac Function

The knowledge of cardiovascular afferent neural mechanisms is of little significance if not considered in concert with the efferent neural mechanisms of

cardio - cardiac reflexes, although recently some investigations have approached this dual problem (22). The efferent autonomic control of the heart on the other hand is well described (20, 105, 106) and since the first elucidation of the autonomic nervous system (42) local control of inotropic, chronotropic, and dromotropic states have been documented (48, 92, 102, 104). For a number of years the autonomic nervous system has been known to effect cardiac function and recently both parasympathetic (109) and sympathetic (102, 104, 105) portions of that nervous system have been demonstrated to effect the chronotropic and inotropic states of the heart (7, 43). Evidence is also available demonstrating that the efferent branches of the autonomic nerves project onto highly localized regions of the heart (106) so that while one region may be augmented in its contractile behavior, another nearby portion of the heart may be unaffected or, indeed even depressed (4, 6, 8). Dynamically one region of the heart can behave quite differently from another in response to a given physiological intervention (4). Pulmonary artery or aortic occlusion augment contractility on the right side of the interventricular septum whereas the left septum is augmented only by aortic occlusion (8) and not at all by pulmonary occlusion. Depression of contractile force in

one papillary muscle can occur while other regions or even other papillary muscles are augmented (6). Thus it is evident that functional regions of the heart (5) behave in quite disparate fashions. Neural control of different regions of the heart may be highly localized and potentially can contribute to highly discrete regional control.

Langley and Anderson (65) demonstrated the presence of autonomic nervous system reflexes in the neural regulating of the urinary bladder. Stimulation of sensory afferents in a somatic nerve has long been known to effect the autonomic nervous system (52); the autonomic nervous system is under the influence of the brainstem (124). Recently ample evidence has been accumulated concerning the direct effects of the efferent autonomic nerves upon cardiovascular receptors, in that afferent traffic from cardiovascular receptors is modulated by efferent neuronal activity (61, 116). Thus the afferent, efferent, and reflex mechanisms exist within the autonomic nervous system along with central modulation (76) to account for highly localized control and interactions of organs supplied by this system. Some Russian scientists have long been concerned with such cardio-cardiac reflexes (62), however the problem has not been clearly resolved. These systems may account in part for the central nervous system especially

spinal and supraspinal regulation of the heart (76, 100, 124), a system which must be involved in the learning behavior which modifies cardiac function (82). As such they are vital in understanding cardiovascular function during physiological as well as abnormal states - a view unchanged since the time of Langley (66).

CHAPTER III

MATERIALS AND METHODS

A. Experimental Preparation

Thirty-two post-absorption mongrel dogs of either sex, weighing from 17 to 25 Kg, were anesthetized with phencyclidine hydrochloride (2 mg/Kg I.M.) and alpha chloralose (80 mg/Kg I.V.). A tracheotomy was performed through a midline neck incision and the vagosympathetic nerves isolated. Positive pressure respiration was accomplished via a tube placed directly into the trachea utilizing a Byrd Mark 7 respirator. The heart and thoracic autonomic nerves were exposed by a bilateral thoracotomy (Appendix I); a standard limb lead II EKG was recorded and PE 50 catheters placed into two of the four cardiac chambers as well as into the arterial tree either in the right internal mammary or right femoral artery. When receptors with afferents in the right thoracic autonomic nerves were analysed, pressures in the right atrium and ventricle were recorded; when left thoracic nerve were

recorded pressures from the left atrium and left ventricle were measured. Femoral arterial or internal mammary arterial pressures were recorded in order to assess systemic pressure. All the pressures were monitored via Statham P23Db strain gauge transducers. The ECG was connected to an Offner 9806 A.C./D.C. coupler and the pressure transducers to an Offner 9803 strain gauge couplers amplification was accomplished with Offner Model 491 amplifiers. The amplified EKG and pressure records were displayed upon a Tektronix 561A single beam four trace oscilloscope for instant analysis and stored upon Scotch Brand 870-1/2-2500 I.R. eight channel magnetic tape via a Precision Instrument (PS-207A) tape recorder. Four FM reproduction channels were employed to record the EKG and pressures at a tape recording speed of 7 1/2 inches per second. Two direct reproduction channels were used to store the nerve recordings (Section B below) as well as an audiosignal on the tape. The audiosignal contained spoken procedural data which assisted in playback. The frequency responses for the direct channels ranged from 50-15,000 Hz, and for the FM channels 0 to 1,250 Hz.

In the experiments in which the right thoracic autonomic nerves were analysed, a thread was attached to a major chorda of the anterior papillary muscle of the right

ventricle during inflow occlusion. The thread was led out of the sutured atriotomy to a pulley whereby the right ventricular anterior papillary muscle - chorda complex could be stretched by adding 5 gm, 10 gm, 15 gm, 25 gm, and 50 gm weights. In each experiment occlusions of the vena cava, pulmonary artery, and aorta (ascending or descending) were performed in order to alter cardiac dynamics. Norepinephrine (0.5 μg/Kg) and isoproterenol (0.05 μg/Kg) were injected into the right atrium in a bolus in order to augment cardiac activity. Propanolol (1 mg/Kg), phentolamine (1 mg/Kg), lidocaine (0.5 mg/Kg) and procaine (0.5 mg/Kg) were also injected via a bolus into the atria to analyse the effects of these drugs on afferent nerve activity.

B. Procedure of Nerve Recording

With the prepared animal in a Faraday cage with one open side, nerves were prepared with the aid of a Zeiss binocular K 90/47 microscope with a capacity of 40 X amplification. Under 10 fold magnification the thoracic autonomic nerves were identified (Appendix I) and dissected free of the thoracic vagus or sympathetic ansa and ganglia, obtaining a nerve segment as long as possible. Sharp dissection was employed to remove neurolemma; a nerve length of two to four centimeters was achieved to minimize motion

artifacts. The dissected nerve was placed in a small oil-filled bath and further dissection performed. The fibrous sheath and epineurium were cut free from the nerve and the nerve dissected into filaments. In some instances these filaments were examined histologically at the termination of the experiment to determine the number of neural elements they contained. Nerves carrying afferent impulses were usually found to be clustered in discrete bundles. The numerous afferent nerves in such a small bundle were then further dissected in order to record single unit afferent activity in accord with accepted criteria this was determined by the height of the electrical activity as well as the timing characteristics of the impulses. A single afferent with a receptor was identified when the afferent impulses had uniform electrical activity (spike height constant), fired with repetitive characteristics, and acted in accord with the receptor location.

The single unit preparation was then placed over two stainless steel electrodes and the electrical activity of the nerve was led to a Grass P9 A.C. preamplifier and then further amplified so that approximately 50 μV input generated a one volt output. This electrical signal was displayed on the Tektronix 561A dual beam oscilloscope coincident with the EKG and pressures from

two locations in order to instantly monitor the experimental results. The nerve action potentials were also led to a direct reproduction channel of the tape recorder for storage along with the EKG and pressure records. Another direct reproduction channel stored the audio information allowing a synchronous record of the experimental interventions and experimental protocol. A loud speaker attached to the neuronal amplifier allowed audio analysis of the nerve action potentials facilitating identification and maximization of the signal to noise ratio of nerve action potentials. Conduction velocities of a number of afferent neurons were also determined (Appendix II).

C. Identification and Localization of a Specific Receptor

For mechanoreceptors local tissue distortion by probing identified their exact localization and for chemoreceptors infusion of potasium cyanide (Ph of 8) (0.025 mg/Kg) into the root of the aorta or local ischemia was employed; incisions were often used to more precisely isolate chemoreceptors. Pulmonary mechanoreceptors were active only during inflation or deflation of the lungs; their behavior was unrelated to the cardiac cycle. These receptors were further localized by minimal local probing of the lung. In addition, sutures were placed on either side of these pulmonary mechanoreceptors and one was fixed while the

other run over a pully in order to add increasing weight and thereby incrementally lengthen the pulmonary tissue surrounding the receptors. Cardiac mechanoreceptors were identified by their neural activity and timing in the cardiac cycle; for instance, ventricular receptors usually fired during ventricular systole, and aortic receptors a little later. These receptors were further localized by their dynamic responses to procedures effecting the atria, ventricles, or great vessels. Finally, discrete localization was accomplished by localized length changes (i.e. touch or stretch). This was readily done in the case of atrial and great vessel receptors, but due to the fact that almost all of the ventricular receptors were endocardial, or more rarely myocardial in location, it was harder to stretch these receptors. Ventricular receptors were usually distorted via a probe placed through an atrial appendage incision. Right ventricular receptors responded to vena cava or pulmonary artery occlusion and left chamber receptors to partial aortic occlusion. Emphasis must be placed on the fact that receptors at the root of the aorta are readily confused with ventricular ones and were identified by local distortion. Although probing of the endocardial surfaces was accomplished through atriotomies which were tightened around the probe,

it was not considered entirely satisfactory. Thus with unusually behaving ventricular receptors or excellent preparations, at the end of an experiment the heart was fibrillated, its apex removed, and the receptor localized by direct distortion. Thus the degree of local deformation effecting a ventricular receptor could be assessed as well as its exact location. Frequently atrial, ventricular, or aortic receptors were removed in block with their surrounding tissue. The functioning of the receptors was then tested and the tissue slowly sliced away from its region in order to assess the receptor field. Microscopic sections stained with hemotoxylin and eosin, were employed to examine histologically the tissue where receptors were localized. Histological sections of the thoracic autonomic nerves were also obtained and stained with hemotoxylin and eosin to determine the cross-sectional diameters of nerves in the predominantly afferent nerves and the number of nerve fibers present in the dissected nerve filaments which contained active afferent nerves.

D. Data Analysis

In each experiment a record sheet was kept outlining the number, localization, and type of receptors analysed. Not all receptor activity was recorded on tape; as the

experiments proceeded and the ease of obtaining afferent nerve recordings increased, only action potentials with excellent signal to noise ratios were stored. Aortic receptors were so numerous and similar in behavior that only a small fraction of the total were retained on tape. The tape was replayed in order to photograph the action potentials, EKG, and pressure records on a Tektronix type 565 dual-beam eight trace oscilloscope; the photographs were accomplished with a Grass model C4N kymograph camera utilizing Kodal 1732 35 mm film or a Polaroid land camera with an Oscillo-Raptar lens (75 mm, f 1.9, 1:0.9 magnification) utilizing a Polaroid 3000 speed type 67 black and white film. The Polaroid pictures and the Kodak strip films were mounted and photographed in order to display important sequences of specific cardiac and pulmonary receptors.

Tabulation of receptors was performed to demonstrate their location and type. This data grouped according to localization identification as well as the nerve in which the afferents were located.

CHAPTER IV

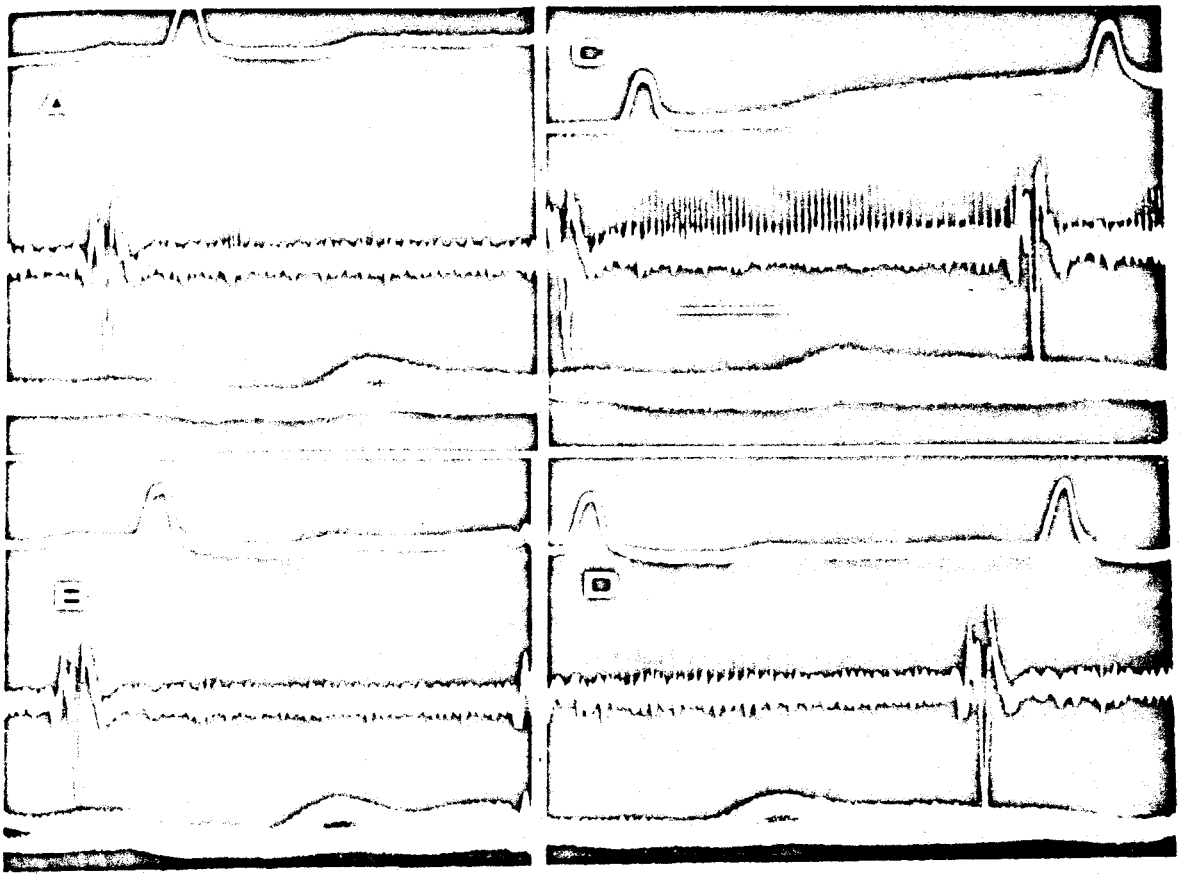
RESULTS

A. Atrial Receptors

Figure 1 illustrates four cardiac cycles (A, B, C, and D). Each panel represents from above downward a limb lead II EKG, right stellate cardiac nerve afferent recording with a "P" wave artifact, as well as below right atrial and right ventricular pressures; the pressures do not change in the four traces. In control states (A and B) this right atrial receptor fired once per systole synchronously with the "S" wave of the EKG or twice, synchronously with the "S" and "T" waves of the EKG, the latter group occurring at the peak of ventricular systolic pressure. Note also that the first group of nerve firing in A contain four impulses whereas the group of impulses in B only has two events. In panel C the same atrial receptor, which covered an area of about one square millimeter in the SA node region was locally distended continuously via 5 grams of force. Note that the

FIGURE 1

SINOATRIAL NODE RECEPTOR



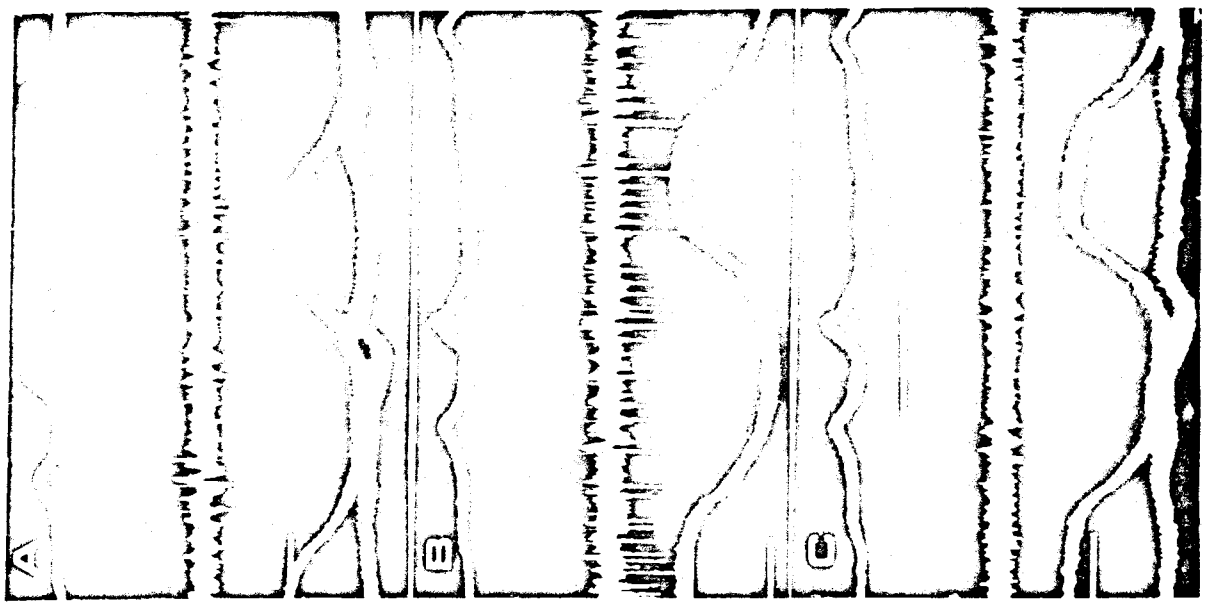
Afferent traffic of a twig from the stellate cardiac nerve was recorded from a receptor in the sinoatrial node. Panel A and B are two control pulses and panel C illustrates activity when the receptor was locally stretched by 5 grams; panel D illustrates the immediate cessation of traffic when the mass was removed with commencement of normal activity during the next systole. A time scale of 100 milliseconds (found in all subsequent cathode ray oscilloscope figures) is given by the horizontal white bar in panel C.

bar in panel C represents 100 msec duration; similar bars in subsequent oscilloscope pictures also represent 100 msec of time. This caused the receptor to fire continuously, reaching a peak of 240 impulses/second during the S-T segment; the maximum frequency was obtained using the shortest interspike interval. Note that the traffic was minimal following the "P" wave, presumably when atrial contraction occurred. In panel D removal of the distending force was followed immediately by cessation of receptor firing.

Figure 2 demonstrates the afferent impulses recorded from the left stellate cardiac nerve. A standard limb lead II EKG, left atrial pressure, and left ventricular pressure are illustrated. The zero pressure marker is partially obscured in A and B, and the calibration mark seen on the left of each panel represents 100 mm Hg for the left ventricular pressure and 20 mm Hg for the left atrial pressure. Panel A was taken during a control cardiac cycle and panel B while 5 cc of saline was rapidly infused into the left atrium (absence of left atrial pressure is due to the fact that the same catheter was used for the pressure record and infusion); panel C was taken in the period immediately following the infusion. This left atrial receptor fired in control periods (A) just

FIGURE 2

POSTERIOR LEFT ATRIAL RECEPTOR



Afferent impulses from a left atrial receptor recorded in the left stellate cardiac nerve are illustrated during control states (A) along with a limb lead II EKG (upper trace), left atrial and left ventricular pressures (lower trace). A zero pressure bar (obscured by the atrial pressure trace in A and C) as well as 100 mm Hg pressure calibration for the LVP are shown; saline was infused into the left atrium during B; the period immediately following the infusion is shown in panel C.

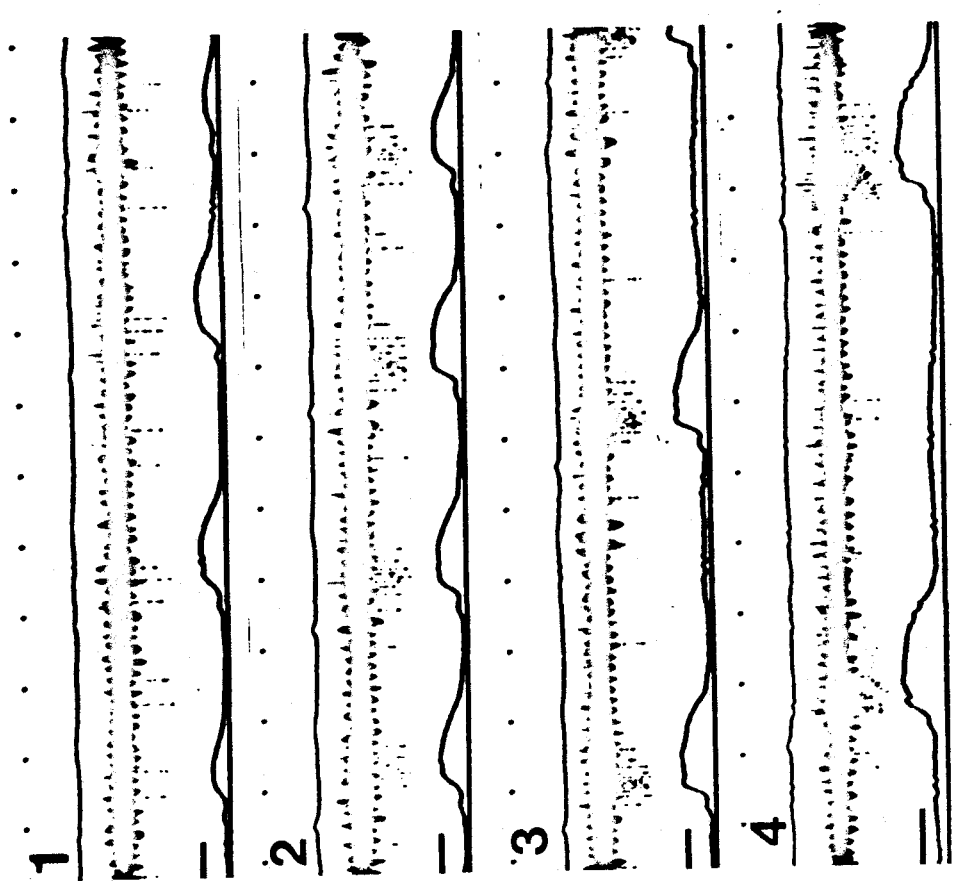
at the beginning of the "P" wave of the EKG, that is just before the "a" wave of the atrial pressure. The same receptor fired maximally throughout atrial distention (B); a second receptor fired during this period as evidenced by the different heights of the two action potentials. When the distention was released (C) the receptor firing ceased and the receptor started to fire only after ten additional systoles. This receptor was localized in an area covering about one square centimeter on the left mid-posterior region of the left atrium near the pulmonary vein orifices; it was sensitive to atrial distortion by the lungs caused by positive pressure inflation.

B. Ventricular Receptors

Figure 3 records the afferent traffic from a branch of the craniovagal nerve. The upper trace is a limb lead II EKG, next the nerve traffic, at the bottom, right ventricular pressure; the zero pressure line is below the pressure trace and the dark bar on the left of each panel represents 25 mm Hg. In panel 1 the nerve traffic occurred in bursts (an average of four impulses per systole) associated with the development of right ventricular pressure although some occurred in diastole. From panels two to four the pulmonary artery was occluded by increasing amounts so that right ventricular pressure was increased

FIGURE 3

RIGHT CONAL RECEPTOR



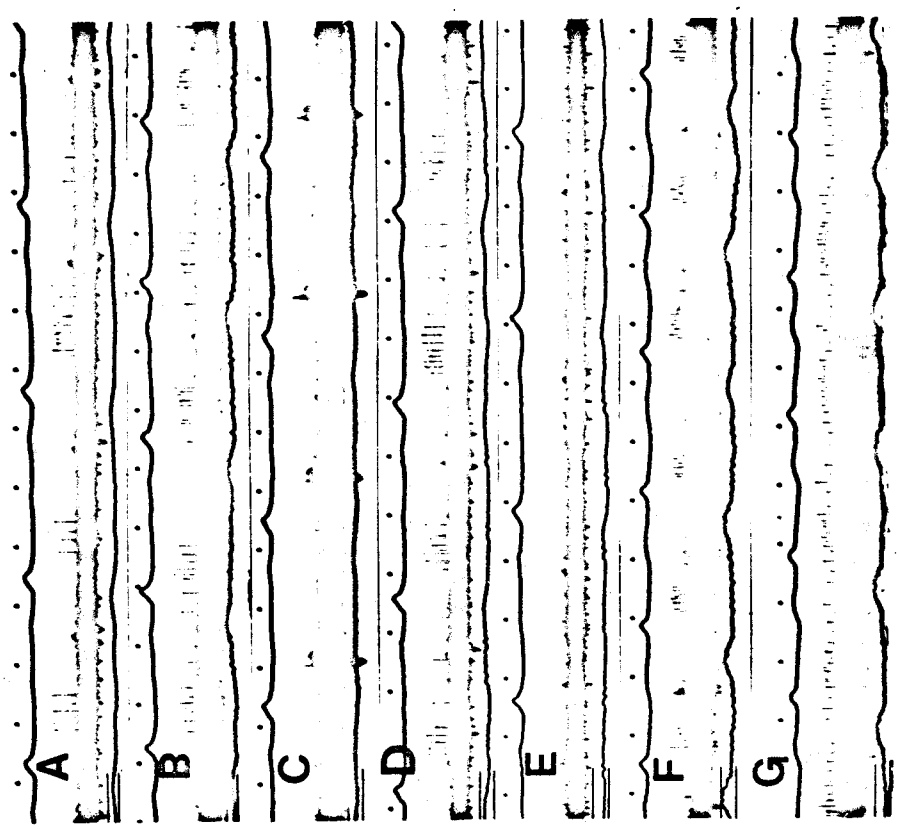
The firing of a conal receptor with its afferent nerve in the craniovagal cardiac nerve, is demonstrated along with an EKG (top trace) and right ventricular pressure (bottom trace) during control states (panel 1) and during progressive occlusion of the pulmonary artery with concomitant bradycardia and rise in right ventricular pressure (panels 2, 3, and 4); note that with peak pressure generation maximal traffic occurred in systole.

from a control value of 18 mm Hg to 24 mm Hg (panel 2), 26 mm Hg (panel 3), and finally to 35 mm Hg (panel 4). Note the concomitant bradycardia as the occlusion was increased. Impulse traffic per systole increased from a control state average of 4 to 5 per systole, to 9 impulses (panel 2), 11 impulses (panel 3), and finally about 24 impulses per systole in panel 4. During pulmonary artery occlusion the impulse traffic was greatly augmented; as the pressure was developed and when peak systole had been achieved the impulse traffic was maximal. This receptor was located via probing on the endocardial surface of the cranial septal region of the right ventricular conus, extending a little onto the lower free wall of the conus. In each panel 100 milliseconds of time occurs between two of the upper dots; the same time markers in subsequent figures represent similar time intervals.

Figure 4 is the record of a limb lead II EKG, afferent impulses from a fiber in the caudovagal nerve, and the lowest trace represents right ventricular pressure; the short dark lines in the lower left of each panel represent a zero pressure and 25 mm Hg calibrations. In control states (panel A) the impulses were generated after the QRS wave of the EKG; every second beat was characterized by afferent traffic of about seven spikes

FIGURE 4

RIGHT VENTRICULAR RECEPTOR



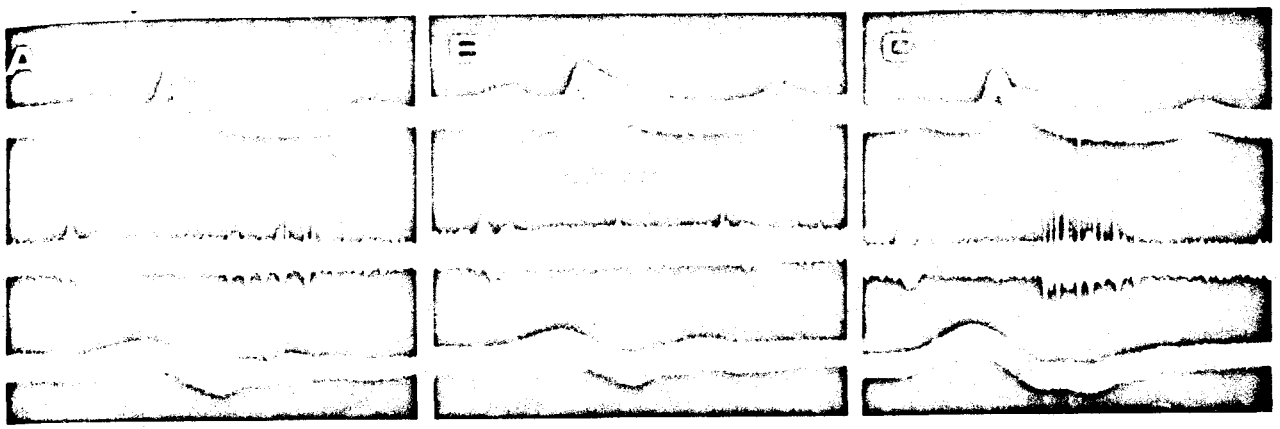
Afferent nerve traffic in the caudovagal nerve from one or more receptors arising from the right ventricle during control states (A), during distention of the right ventricular papillary muscle (B), release of that distention (C), pulmonary artery occlusion (D), inferior vena cava occlusion (E), isoproterenol augmentation (F), and finally following an injection of norepinephrine (0.5 µg/Kg) (G). The limb lead II EKG, nerve traffic, right ventricular pressures are located from above downward in each panel. Zero and 25 mm Hg pressures are marked by bars in the left of each panel. Above each panel are time markers spaced at 100 millisecond intervals; all subsequent figures employing strip films will have the same time markers.

per cycle, while alternating beats were accompanied by about three impulses per systole - a form of impulse alternans. Immediately prior to panel B twenty grams were added to the anterior papillary muscle - chorda complex and this was removed between B and C, there was an increase in impulse traffic to 12 impulses per systole with the weight added, and a cessation of impulses when it was removed. In panel D the pulmonary artery was partially occluded and the traffic rose to an average of 15 impulses per systole; panel E demonstrates the abolition of impulse traffic after the inferior vena cava was occluded. The augmentation of contraction produced by infusion of isoproterenol (panel F) generated an increase of traffic to eight impulses per systole; these impulses were confined to the period of peak ventricular systole. Noradrenaline (panel G), on the other hand augmented impulse traffic throughout systole and diastole, the maximal traffic occurring once more between the QRS and "T" waves of the EKG with an average of 22 impulses per cycle.

Figure 5 represents during single cardiac cycle a standard limb lead II EKG, nerve action potentials recorded in a branch of the recurrent cardiac nerve, and a left atrial pressure record from above downward. During control periods (A) there were 5 impulses per systole which

FIGURE 5

RIGHT VENTRICULAR PAPILLARY MUSCLE RECEPTOR



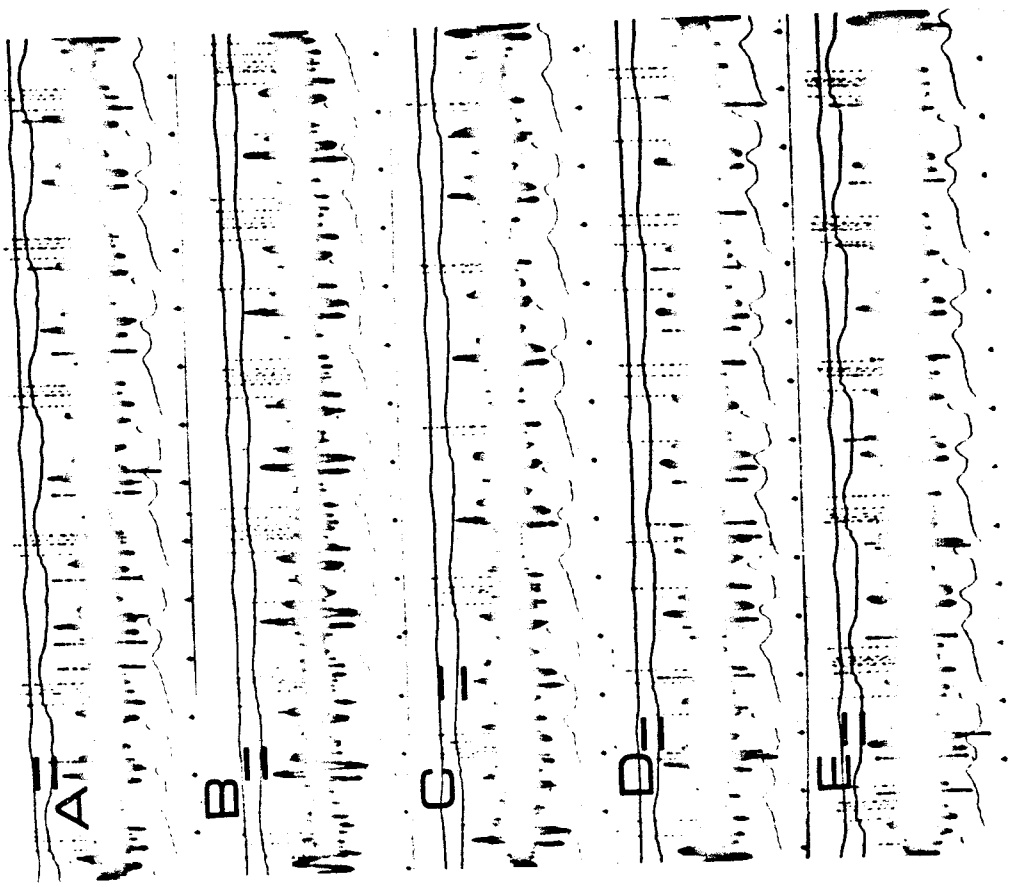
A right ventricular receptor located near the anterior papillary muscle had its afferent nerve in the recurrent cardiac nerve; its activity is recorded along with a limb lead II EKG, and right atrial pressure during control states (A), distention of the papillary muscle (B), and following cessation of that distention (C). Note that on removal of the weight receptor fire which were silent in control states (note difference spike heights in panel C).

occurred between the QRS and "T" waves of the EKG; these were entirely abolished with 20 grams distention of the right ventricular anterior papillary muscle (B). Upon release of the distending force (C) the impulse traffic was increased to 10 impulses per systole.

Figure 6 shows afferent traffic recorded from a branch of the recurrent cardiac nerve along with right atrial pressure (upper trace), right ventricular pressure (below right atrial pressure) and a limb lead II EKG (lowest trace); the black bars represent zero pressure and 25 mm Hg calibration for the right ventricular pressure. In control states (A) the impulse traffic was clustered after the "S" wave of the EKG, averaging four impulses per systole. In panel B twenty grams had been added to the anterior papillary muscle and impulse traffic increased to 9 per systole, 1 occurring in diastole. In panel C the weight was removed after the first systole; note the immediate decrease of traffic to 2 per systole. In D the inferior vena cava was occluded by a thread and reduced impulse traffic was distributed over a larger period of time during each cardiac cycle. Finally in panel E, when the pulmonary artery was partially occluded and peak right ventricular pressure increased, the impulse traffic was increased to 6 or 7 per systole, the

FIGURE 6

RIGHT VENTRICULAR PAPILLARY MUSCLE RECEPTOR



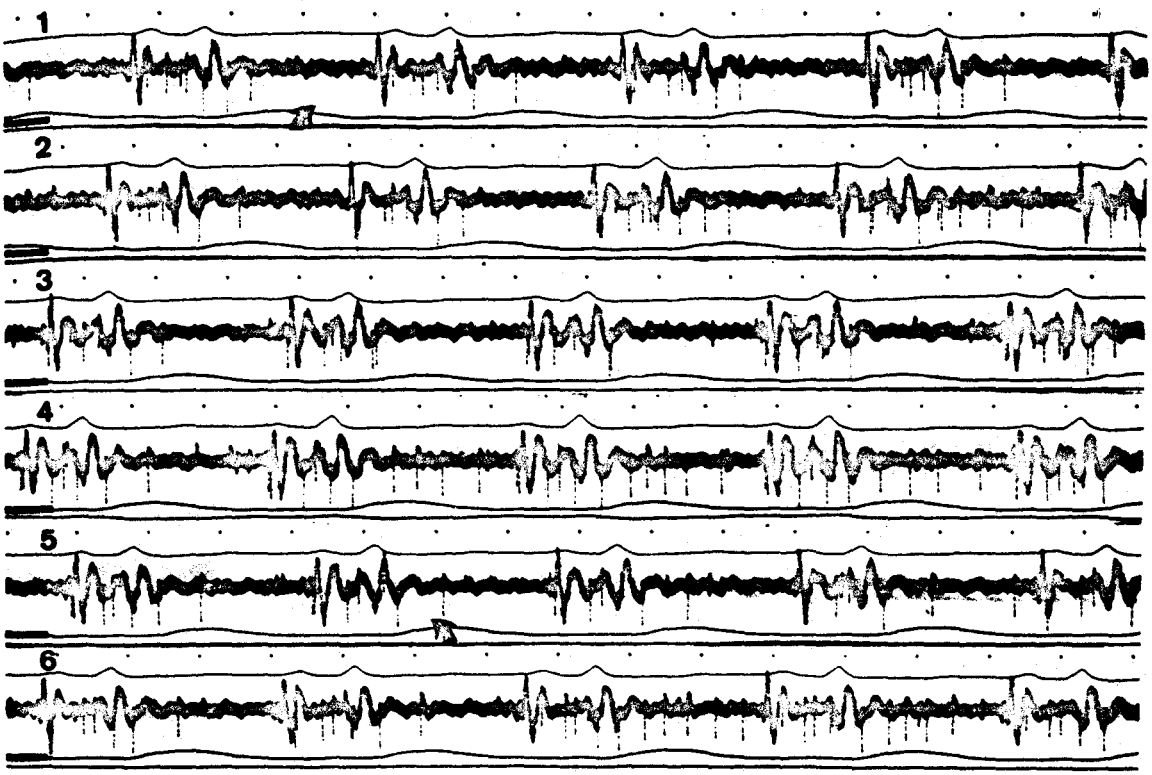
A continuous record of a right ventricular receptor with traffic in a branch of the recurrent cardiac nerve is illustrated (third line from the top of each panel) along with right atrial and right ventricular pressures (top two traces) and a limb lead II EKG (bottom trace) during control conditions (A), after distending the papillary muscle (B), removal of the papillary muscle distention (C), occlusion of inferior vena cava (D), and partial occlusion of the pulmonary artery (E).

traffic being clustered at peak systolic pressure. This receptor was localized by probing at the base of the anterior papillary muscle spreading onto the right septal wall.

Figure 7 represents an afferent nerve recording from a branch of the recurrent cardiac nerve along with a limb lead II EKG (upper trace) and right ventricular pressure (lowest trace). Nerve impulses began concurrent with the peak of the "P" wave (just after the first artifact on the nerve record trace) and were spread to the beginning of the "T" wave, 5 or 6 impulses occurring per cycle. At the arrow in panel 1, 50 grams distended the right ventricular anterior papillary muscle - chorda complex; note that not only did this procedure increase the impulse traffic (11 impulses per systole), but the time of the first impulse gradually advanced in relation to the "P" wave until it began at the start of the "P" wave (panel 4). When the weight was removed (arrow in panel 5) the initial impulses became delayed in relation to after the "P" wave (end of panel 6) and in later sequences returned to 5 or 6 impulses per cycle following the "P" wave. Right ventricular pressure was constant throughout demonstrating no gross valvular incompetence. This receptor was located over a fairly large endocardial zone

FIGURE 7

RIGHT VENTRICULAR PAPILLARY MUSCLE RECEPTOR



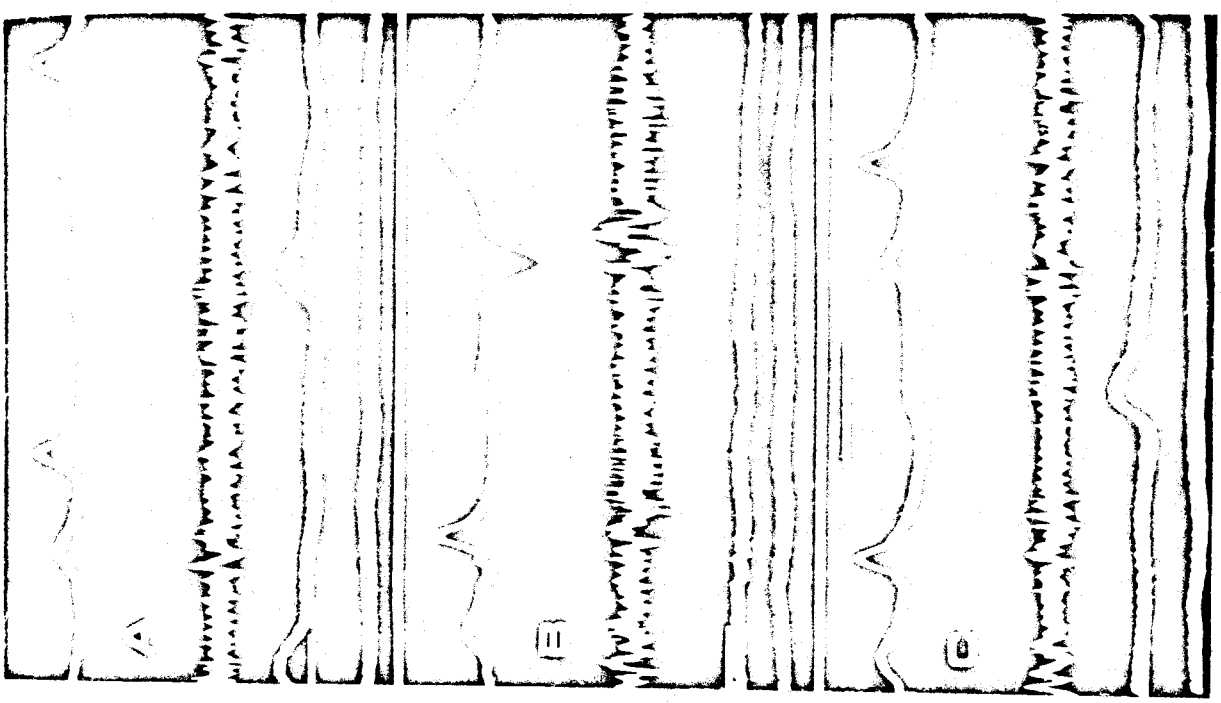
Afferent traffic of a right ventricular receptor which arose from a twig of the recurrent cardiac nerve is illustrated along with a limb lead II EKG (upper trace) and right ventricular pressure (lowest trace) before, during (between arrows), and after distention of the right ventricular anterior papillary muscle. Note that during distention of the papillary muscle, not only is there increased traffic but the first spike in each group advances from a time after the "P" wave until it precedes it in time.

of the right ventricular septum below the tricuspid valve and extending past the anterior papillary muscle.

Figure 8 demonstrates afferent traffic in a twig of the craniovagal nerve (middle trace) along with a limb lead II EKG (upper trace), and internal mammary and left atrial pressures (lower trace). During control contractions 4 impulses clustered after the QRS wave of the EKG can be clearly seen. During occlusion of the root of the aorta, with the systemic pressure falling, the receptor fired 11 times per ventricular systole except when a ventricular premature contraction developed (right side of panel B); with a poorly coordinated contraction the impulse traffic was reduced to 2 per systole. Upon return to control states (C) the nerve traffic returned to only 3 impulses per systole. In Figure 9 another left ventricular receptor with its afferent fiber in the innominate nerve is shown along with an EKG and left atrial pressure. In control states there were 4 impulses per ventricular systole all within the ST time segment of the EKG. During occlusion of the ascending aorta (B) the traffic increased to 8 or 9 per systole. After ventricular fibrillation (C) and the removal of the ventricular apex, this receptor was located in the endocardium of the left ventricular septum covering a zone of

FIGURE 8

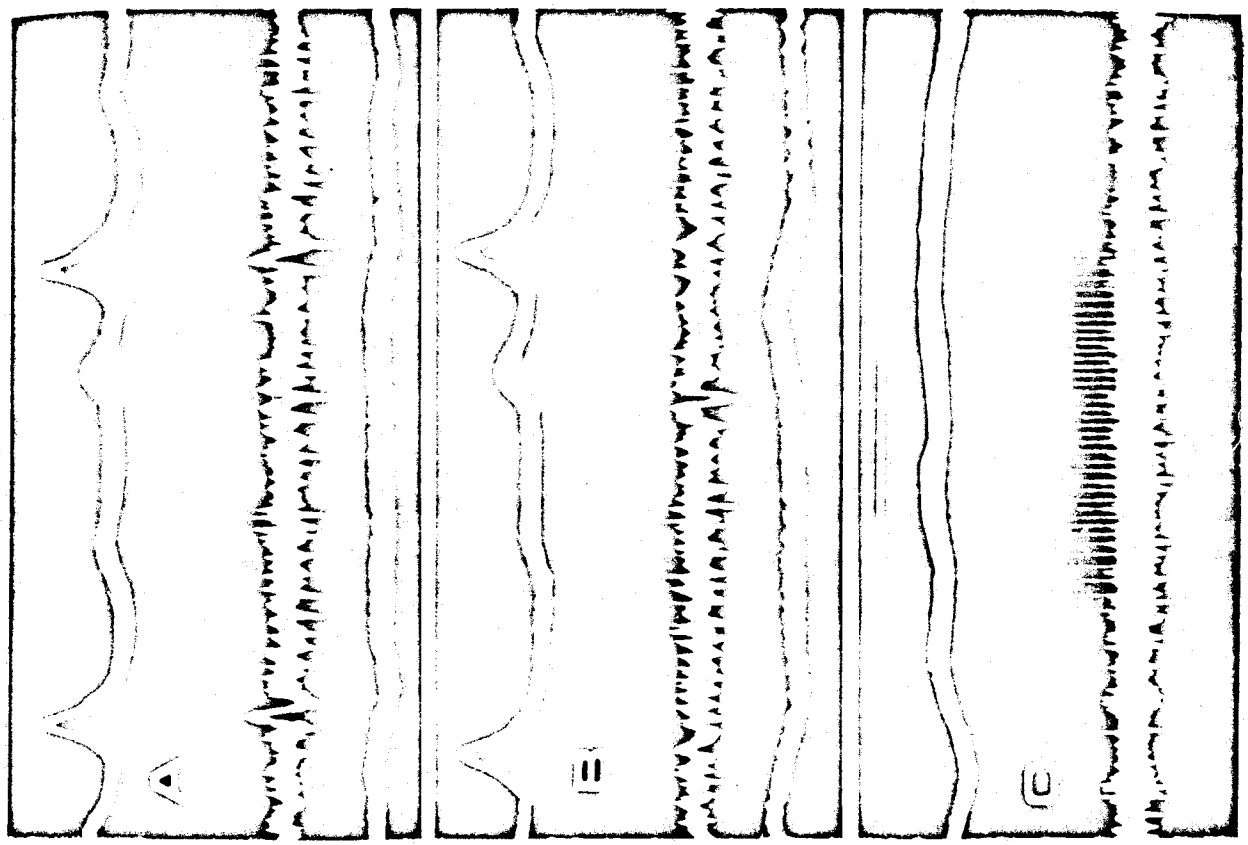
LEFT VENTRICULAR RECEPTOR



An EKG, craniovagal nerve afferent activity from a left ventricular receptor, and femoral artery as well as left atrial pressures are demonstrated for control states (A), during partial occlusion of the ascending aorta (B), and immediately post-occlusion (C). Note that with aortic occlusion and the accompanying increased contractility of the ventricle the receptor activity was augmented (except during ventricular premature contractions). The zero pressure bar is obscured by the atrial pressure record and the 100 mm Hg pressure bar is on the left of each panel.

FIGURE 9

LEFT VENTRICULAR SEPTAL RECEPTOR



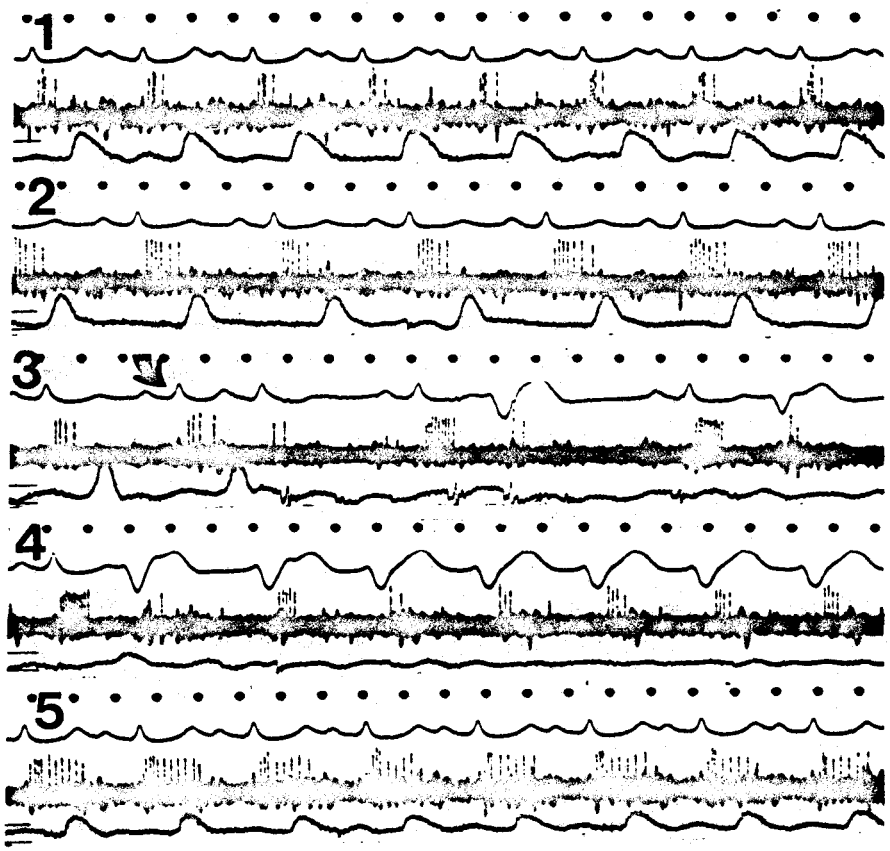
A left ventricular receptor activity during systole, with its afferent fiber in the innominate nerve, is shown along with an EKG and left atrial pressure during control states (A), partial occlusion of the ascending aorta (B), and during fibrillation when it was mechanically distorted (C).

about 1 square centimeter in shape, the center of which was 1 1/2 centimeters below the aortic ring. Touching the receptor with a hair elicited the response in panel C; this response to mechanical stimulus persisted at least 15 minutes (after fibrillation was initiated).

Figure 10 shows the afferent impulses recorded from a slip of the recurrent cardiac nerve, along with a lead II EKG (upper trace) and aortic pressure; the two thin lines on the left of each pressure trace represent 50 and 100 mm Hg. During control states (panel 1) there was an average of 4 impulses per systole, the first impulses being clustered together early in the period of the S-T segment. During occlusion of the distal aorta (panel 2) (note slight increase of systemic pressure and bradycardia) traffic was increased to 7 impulses per systole. Upon occlusion of the aortic root (arrow panel 3), with the concomitant fall in systemic pressure, the impulse traffic increased to eleven impulses per systole when normal electrical excitation occurred; however with the development of ventricular ectopic foci (panels 3 and 4) the traffic per systole was greatly diminished. With augmentation of contractility via isoproterenol (panel 5) the impulses per systole not only increased but the impulse generation (which occurred early in systole) achieved its

FIGURE 10

LEFT VENTRICULAR RECEPTOR



A left septal receptor with its afferent nerve in the recurrent cardiac nerve is illustrated along with an EKG (upper trace), and aortic pressure (lowest trace) during control periods (1), coarctation of the descending aorta (2), coarctation of the ascending aorta starting at the arrow in panel 3 and continuing into panel 4, and following the injection of isoproterenol (0.05 µg/Kg) (5).

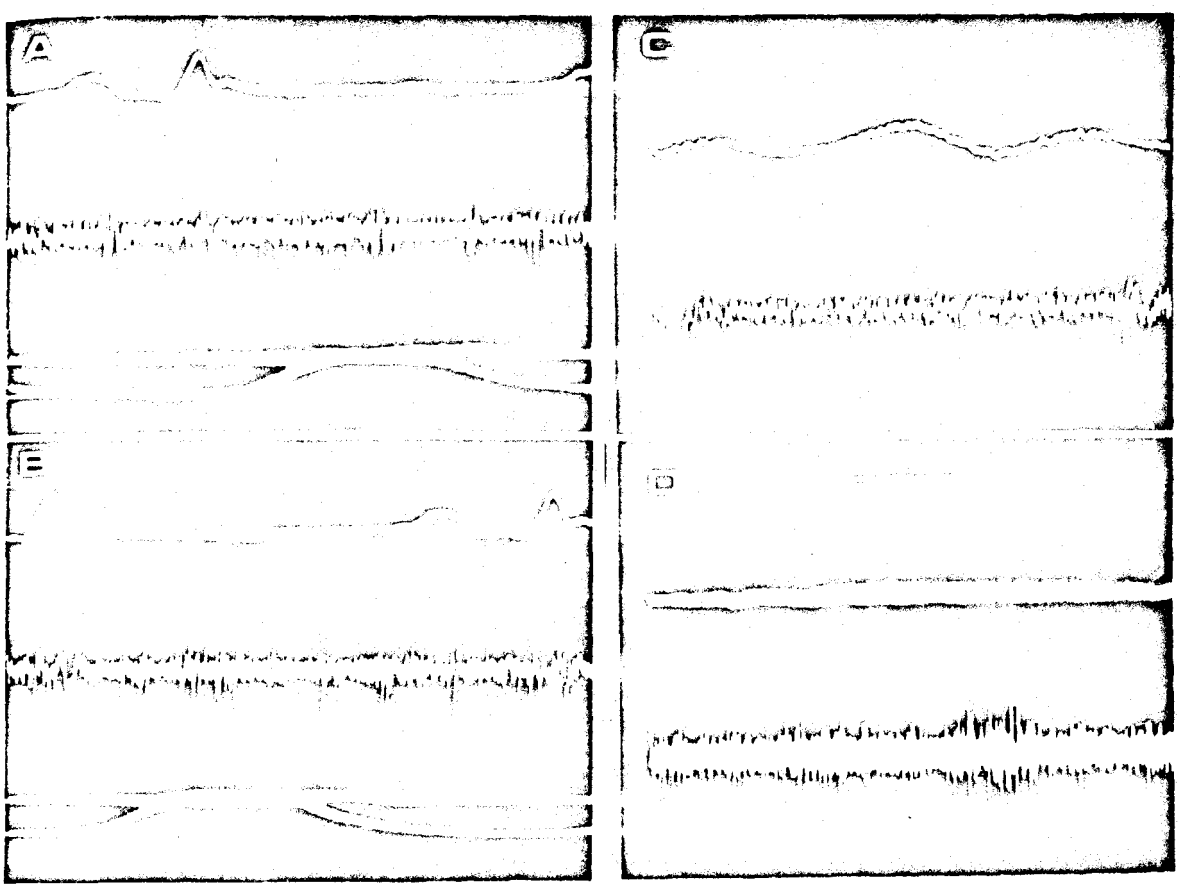
highest rate. This is in contrast to the impulse traffic during afterload augmentation (panel 2). This receptor was localized in the upper mid-left ventricular septum covering an area of tissue of about a square centimeter in form.

Figure 11 illustrates a limb lead II EKG (upper trace), afferent impulses in a twig of the ventromedial nerve, as well as femoral arterial and left ventricular pressures. The zero and 100 mm Hg pressure calibrations are obscured in the left of panels A and B by the pressure waves. This ventricular receptor fired throughout ventricular systole and diastole but fired maximally during the duration of the S-T segment. With minimal occlusion of the descending aorta (B) impulse traffic increased from a control of 15 impulses to 24 impulses per systole. Following ventricular fibrillation (C) the receptor traffic was absent (the nerve recording amplitude was doubled in panels C and D); however upon touching the posterior endocardium 1 centimeter below the junction of the aortic and mitral rings firing was initiated (D). The amplification of the nerve recording was increased for clarity in panels C and D.

Figure 12 shows the afferent traffic from a branch of the recurrent cardiac nerve along with an EKG. During

FIGURE 11

LEFT VENTRICULAR RECEPTOR



A left ventricular receptor afferent traffic in the ventromedial nerve along with an EKG, left ventricular pressure and femoral artery pressure is illustrated during control conditions (A) and following slight occlusion of the aorta (B). The zero and 100 mm Hg calibration lines are obscured on the left of these panels. In C and D the ventricle was fibrillating and pressure records discontinued; during fibrillation the length receptor was silent (C) unless mechanically distorted (D).

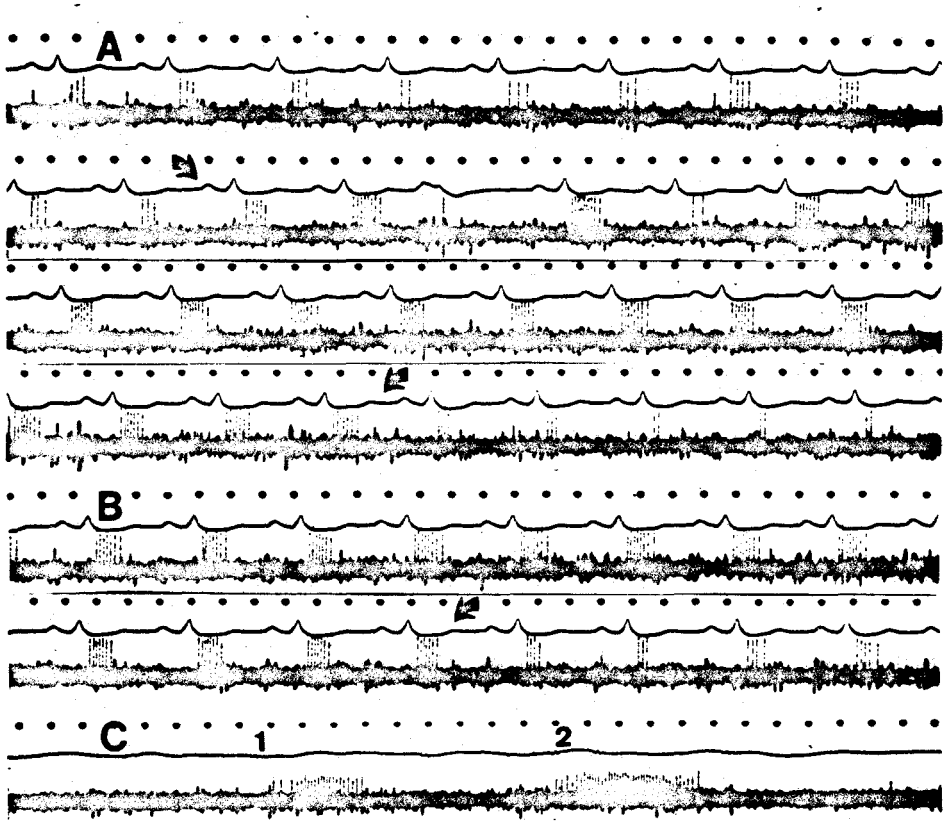
control conditions (panel A) 2 to 4 impulses occurred per systole in the S-T segment. At the first arrow the aorta was partially occluded and released at the second arrow. During the aortic occlusion impulse traffic increased to 11 impulses during normal electrically excited systoles but during spontaneous ventricular ectopic foci was reduced to 1 or 2 impulses. Following release of this occlusion the receptor returned promptly to its control firing level or below. During pulmonary artery occlusion (panel B), traffic was augmented to a maximum of 8 per systole; after release of pulmonary artery occlusion (arrow in panel B) the traffic fell to control levels. During ventricular fibrillation and removal of the ventricular apices (panel C) the receptor was silent; touching an area of the cranial centimeter of the right (1) as well as the left (2) septum initiated impulse traffic in this same preparation; the amplitude of the nerve impulses were less due to the fact that the nerve moved on the electrode during the fibrillation and apical sectioning.

C. Vascular Receptors

Figure 13 represents typical records obtained from afferent impulses carried in the total dorsal cardiac nerve of two different animals. During control states (panels A

FIGURE 12

BILATERAL VENTRICULAR SEPTAL RECEPTOR

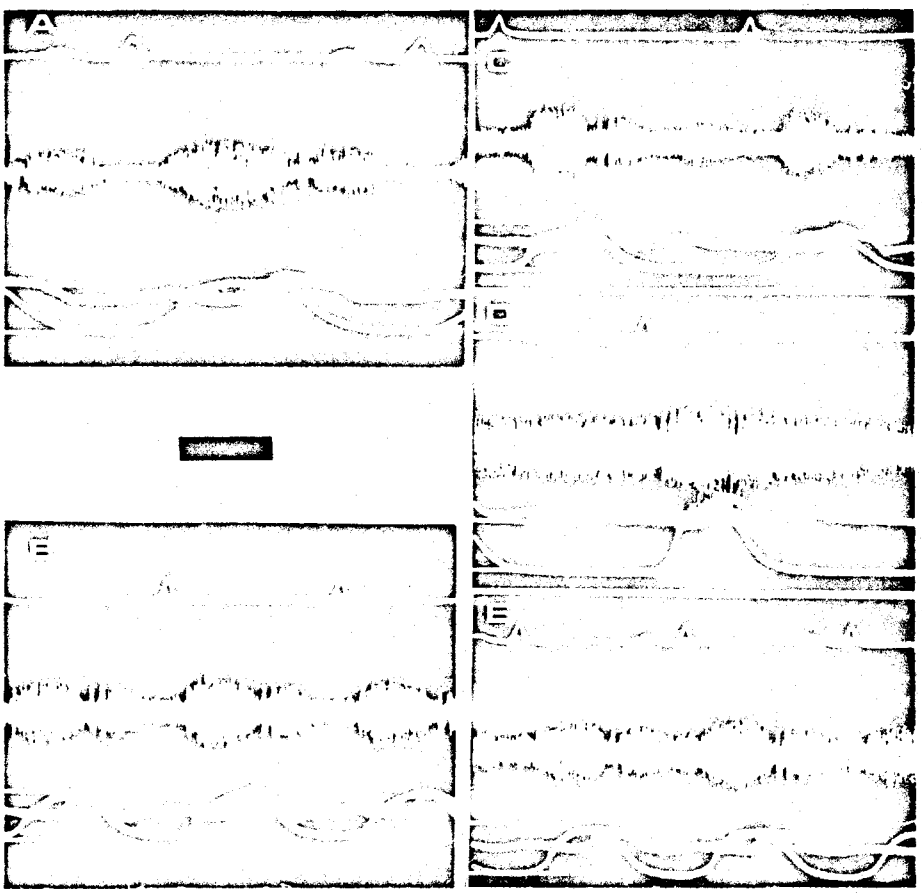


A ventricular receptor with nerve traffic recorded from the recurrent cardiac nerve during control periods, during occlusion of the aorta (between arrows in section A), and post-occlusion. Panel B illustrates the receptor during pulmonary artery occlusion and after release of the occlusion (arrow). In panel C, upon exposure of the ventricular septum during fibrillation, the upper right (1) and upper left (2) septa were gently touched. A standard EKG also is demonstrated.

and B) the limb lead II EKG is shown in the upper trace, nerve traffic in the next trace, and the lower two traces represent femoral arterial and left ventricular pressures. During control conditions the dorsal cardiac nerve had 3 (A) or 4 (B) distinct "waves" of afferent activity, representing the summation of the activity of individual fibers. There was a major wave accompanying systole, one with the dicrotic pressure "notch," and another during the diastolic run off; frequently a small burst of activity occurred as a fourth wave just before systole began (panel B). Panels C, D, and E represent changes in the same preparation as in B. When the thoracic vagi were reflexly stimulated (lung stretch) (C) and the heart rate and systole pressures were reduced, the fourth impulse "wave" was accentuated and a fifth "wave" became evident; note that the femoral artery pressure record in panel C demonstrated 4 waves. After left thoracic vagus section and the concomitant augmentation of systolic pressure (panel D peak pressure of 146 mm Hg as compared to 100 mm Hg for control periods) the nerve traffic was increased so that it was continuous, although being still maximal during systole. Following bilateral cervical vagotomy (panel E) there was an increase in heart rate with little change in systolic pressure; however now the nerve traffic had

FIGURE 13

TOTAL DORSAL CARDIAC NERVE AFFERENT ACTIVITY



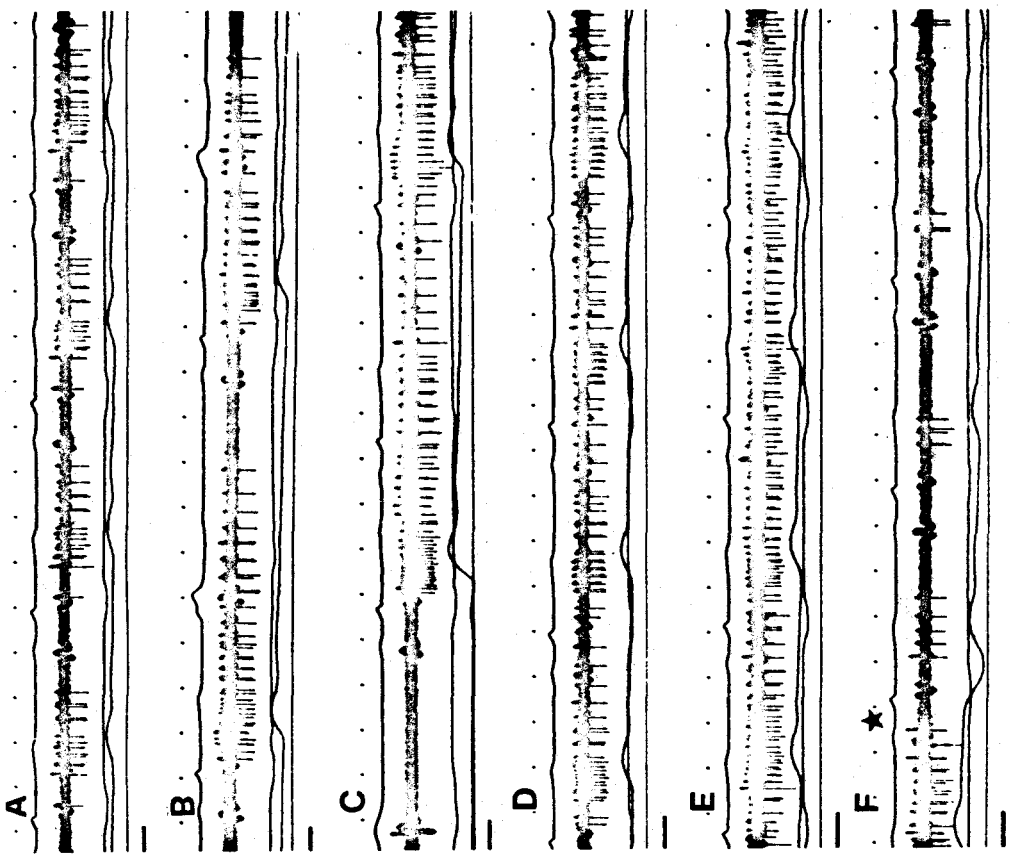
Whole dorsal cardiac nerve activity is shown during control conditions for two different experimental animals (panels A and B); the dark line between these panels is 100 milliseconds of time. Each panel contains an EKG, nerve activity, aortic and left ventricular pressures. The zero and 100 mm Hg calibration for pressure are shown as white bars on the left of each panel. Traces were obtained for the same experiment as in B when the vagi were reflexly stimulated (C), when the vagi were sectioned (D), and post-vagotomy (E). Note the presence of these distinct waves of whole nerve activity in control conditions.

4 distinct "waves" of afferent traffic. The wave of traffic accompanying the dicrotic notch always had the shortest duration.

Figure 14 represents the afferent traffic from a branch of the recurrent cardiac nerve along with a limb lead II EKG, right atrial pressure and aortic arch pressure (lowest trace). Panel A is a control sequence in which the receptor, located in the dorsal aspect of the ascending aorta 1 cm above the aortic ring, fired during the rising pressure phase and ceased during the period of the dicrotic notch only to continue firing during diastole; note that the pressure trace, because of the location of the catheter is delayed in relation to neural activity; in panels B and C the ascending aorta above the receptor was partially occluded, every second beat generating flow into the aortic arch. The receptor fired only during these systoles which generated sufficient aortic pressure to overcome all resistance and thus distort the receptor region; with rapid rates of pressure generation as well as augmented peak pressures firing was augmented so that it was continuous throughout systole and diastole (C). When the distal aorta was occluded by increasing amount (panels D and E) the receptor fired with increasing frequencies. The maximal rate of firing was less than that which

FIGURE 14

AORTIC ROOT RECEPTOR



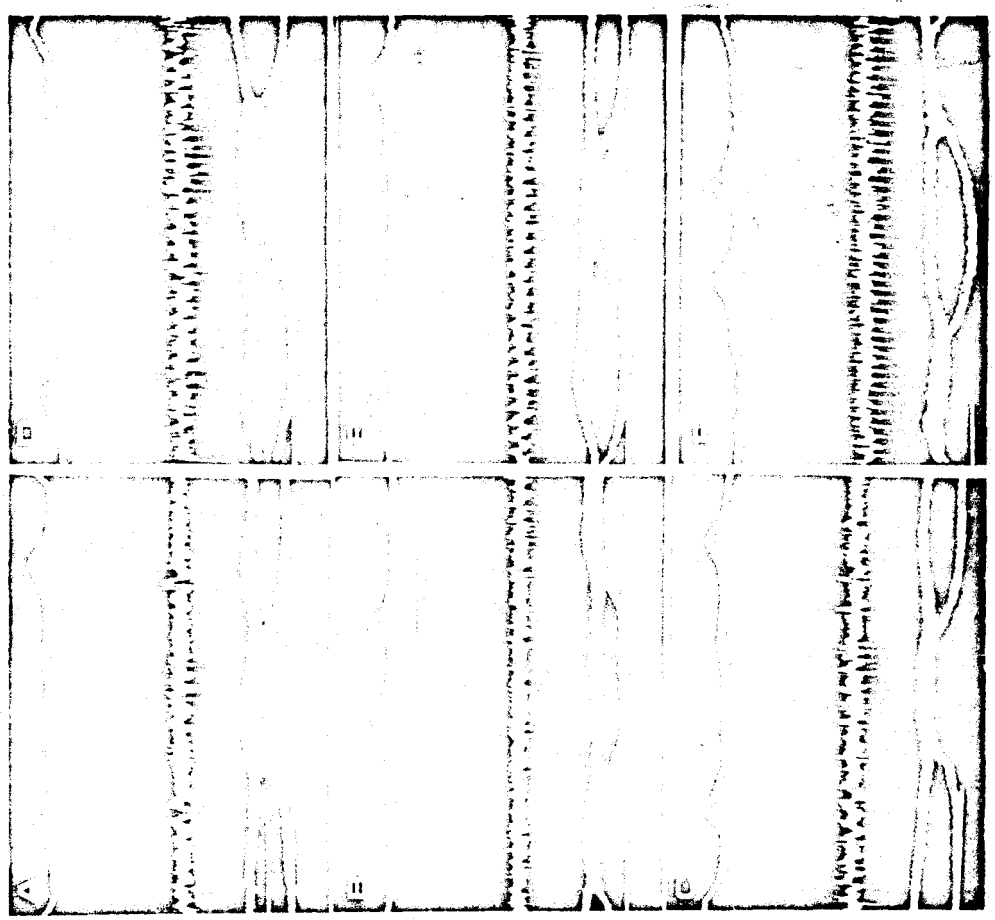
Afferent traffic in a branch of the recurrent cardiac nerve responded to dynamic changes in the ascending aorta as the receptor was located one centimeter from the root on the anterior surface. The upper trace is an EKG, next the nerve traffic, below is the right atrial pressure, and the lowest trace the aortic arch pressure. Note that the bar in the lower left of each panel represents zero pressure and the line across the trace (lowest line) is 50 mm Hg calibration for the aortic pressure. Panel A is a control sequence; panels B and C demonstrate the effects of ascending aorta occlusion, while panels D, E, and F the period of descending aorta occlusion, the occlusion being released at the asterisk in F.

occurred with rapid rates of pressure change during proximal aorta occlusion (panel C) even though equal or even greater peak pressures were achieved. Following release of the distal aortic occlusion (asterisk in panel F) the aortic pressures returned to levels just at or below control values; during that time the impulse traffic generated by the receptor was considerably less than control levels.

Figure 15 illustrates afferent traffic recorded in the dorsal cardiac nerve from a receptor located on the inner curvature of the aortic arch; the receptor covered an adventitial area of 0.5 cm by 0.3 cm. During control states (panel A) a lead II EKG as well as left ventricular and aortic pressures are shown accompanied by the receptor activation during systole as well as following the dicrotic notch. When the descending aorta was progressively occluded by increasing amounts (panels B, C, and D) with minimal change in systolic pressure, there was a dramatic increase in nerve traffic; in panel D the nerve traffic was constant throughout diastole as well as sytole with a maximum firing rate of 125 impulses per second during systole. The receptor fixed on either side by sutures, was stretched by 5 (E) and 10 (F) grams; 5 grams distention caused a continuous impulse traffic of 80 impulses per second and 10 grams of 125 impulses per second. Blood pressure in E and F were

FIGURE 15

ASCENDING AORTA RECEPTOR



An aortic receptor afferent traffic in the dorsal cardiac nerve is illustrated along with an EKG, as well as aortic and ventricular pressures during control conditions (A) and progressive occlusion of the descending aorta (B, C, D). This receptor was locally distended with 5 grams (E, the removal of the weight being shown at the arrow) and 10 grams (F) force.

the same as control. Note that when the weight was removed (arrow in panel E) the traffic was instantaneously returned to control firing rates.

D. Pulmonary Receptors

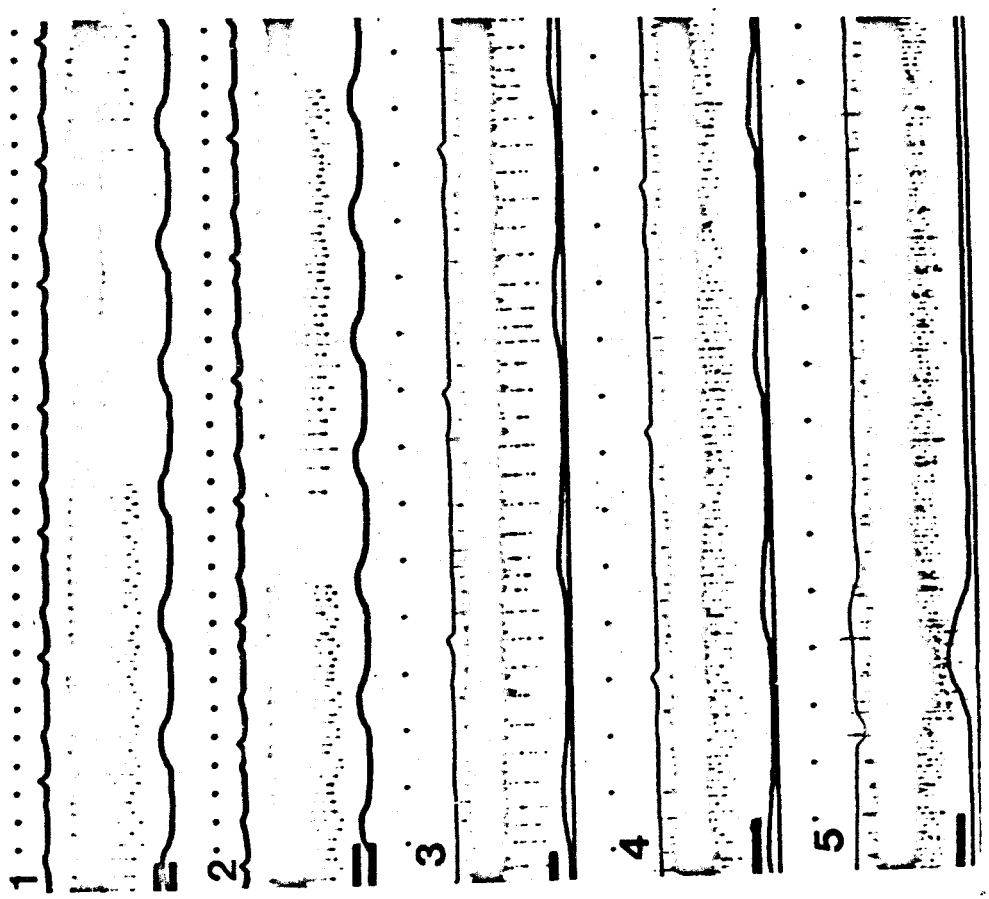
The first two panels in Figure 16 represent a pulmonary inflation receptor along with a standard limb lead II EKG and a right ventricular pressure trace (lowest record). As the respiratory rate was increased (in panel 2 the inflation is shorter and more frequent than panel 1) the rate of receptor firing was increased. This receptor was located in the left lower lobe hilus and upon local distortion (panel 3) fired at a maximal rate of 85 impulses per second.

E. Chemoreceptors

The lower half of Figure 16 demonstrates a cardiac chemoreceptor with its afferent in a different twig of the recurrent cardiac nerve from panels 1 and 2; this constantly firing receptor (panel 3) is shown after thirty seconds of respiratory cessation (panel 4) and fifteen seconds after the infusion of cyanide into the aortic root (panel 5). During control conditions the nerve impulse traffic fired regularly at a rate of 30 impulses per second. After thirty seconds of cessation of respiration (panel 4) the impulse traffic had increased

FIGURE 16

PULMONARY INFLATION RECEPTOR AND
CARDIOVASCULAR CHEMORECEPTOR



The afferent nerve activity of a respiratory inflation sensitive receptor recorded from the recurrent cardiac nerve is illustrated while respiration was driven at two different rates (1 and 2). In the lower three panels a chemosensitive receptor is demonstrated during control conditions (panel 3), after 30 seconds of respiratory cessation (4), and during cyanide stimulation (0.025 mg/Kg) (5). In all panels an EKG as well as right ventricular pressures are recorded; zero pressure (lower line or bar) placed in the left of each panel. Timing dots are 100 milliseconds apart.

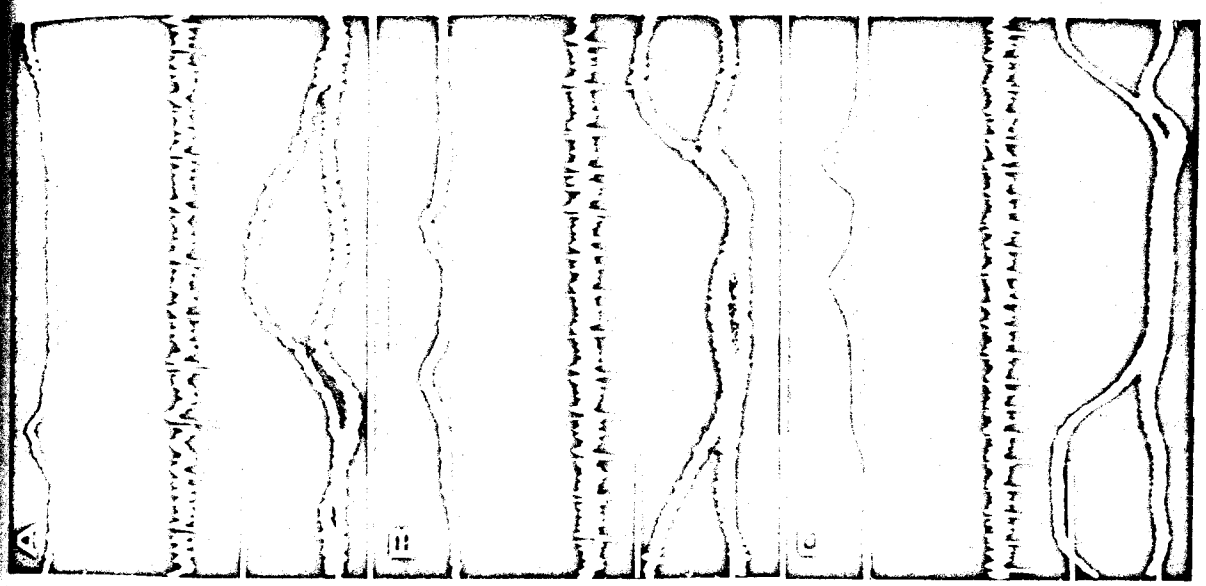
to 70 impulses per second. Immediately following the infusion of cyanide this receptor traffic increased until after fifteen seconds its rate had increased to 120 impulses per second; note the bradycardia in panel 5 and that now during ventricular systole (panel 5) another receptor fired.

Figure 17 represents in each panel from above downward a limb lead II EKG, nerve action potentials in a branch of the innominate nerve, and pressures from the left ventricle and left atrium. In control states (panel A) this receptor fired continuously at a rate of 30 impulses per second; after thirty seconds anterior descending coronary artery occlusion (panel B) traffic increased to 40 impulses per second. Following a minute of 56 impulses per second with a minimal increase of peak systolic pressure.

Figure 18 demonstrates impulse traffic from two continuously firing receptors with afferents which travelled in the innominate nerve. During control periods (panel A) a limb lead II EKG (upper trace), nerve action potentials, as well as aortic and left ventricular pressures were recorded. The two chemoreceptors have different firing rates and different action potential heights most readily evident in C where impulse rates were low.

FIGURE 17

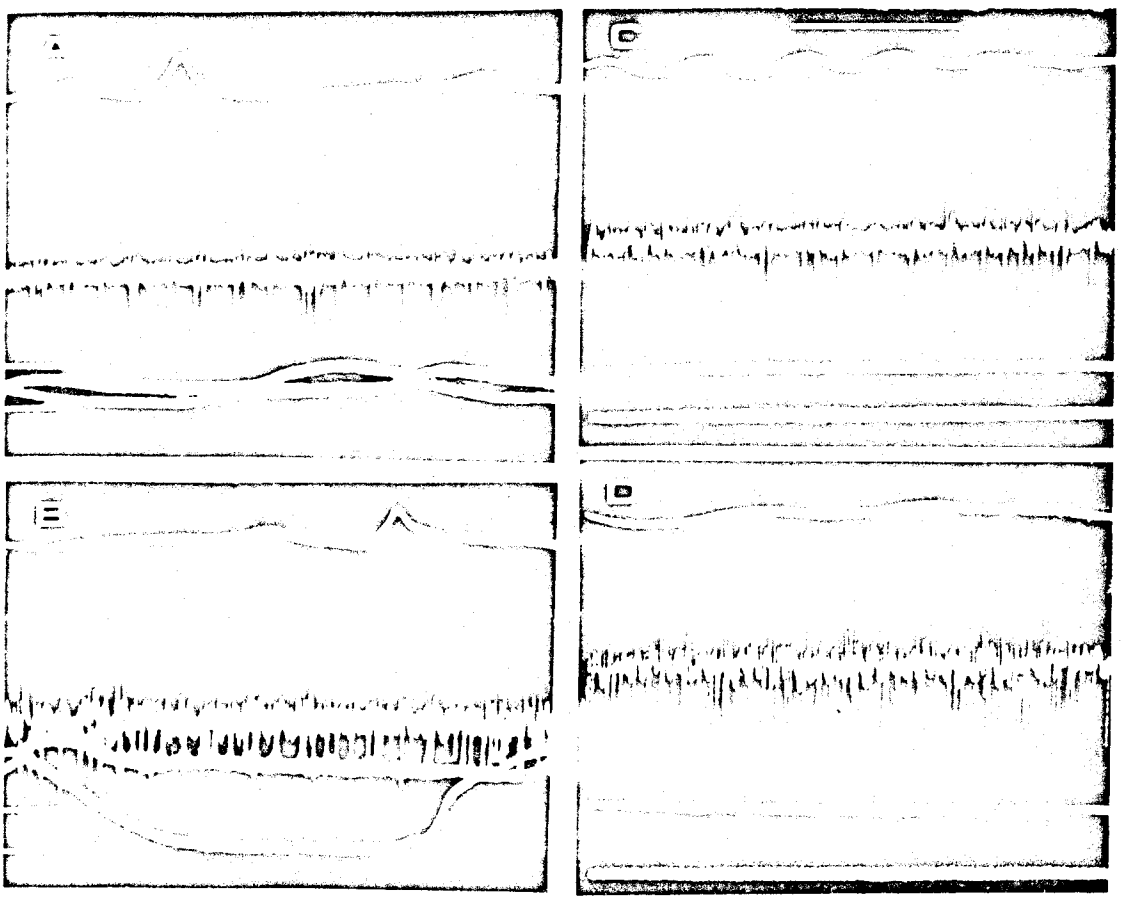
CARDIAC CHEMORECEPTOR



A chemosensitive receptor with afferent traffic in the innominate nerve is shown along with an EKG (upper trace) as well as left atrial and left ventricular pressure (lower traces) in control conditions (A). The zero pressure line is obscured by the atrial pressure, however the 100 mm Hg pressure line is evident on the left of each panel. Panel B, with its 100 milliseconds time marker, illustrates artery occlusion. Panel C represents the receptor response to one minute of hypoxia.

FIGURE 18

AORTIC ROOT AND VENTRICULAR SEPTAL
CHEMOSENSITIVE RECEPTORS



Two chemoreceptors with afferents in the innominate nerve are illustrated with an EKG, left ventricular pressure and femoral artery pressure during control conditions (A) and following cyanide injection (0.025 mg/Kg) (B). At the beginning of fibrillation (C) the receptors fired at the same rate as during control condition, however after one minute of fibrillation (D) the traffic had greatly increased.

That chemoreceptor with the higher action potential height fired at a rate of 80 per second. Following cyanide infusion (panel B) with the usual bradycardia and systolic augmentation, its impulse traffic was augmented to a rate of 120 impulses per second. At the beginning of cardiac fibrillation (panel C) the same receptor fired at a rate of 55 impulses per second; however, after a minute of fibrillation (panel D) this traffic had increased to a rate of 140 impulses per second. Utilizing surgical incision the two receptors were located, one in the cranial centimeter of the mid septum and the other in the first 5 millimeters of the medial aortic root.

F. Summary

Table I lists the location and type of receptors with afferents which coursed in the right thoracic autonomic nerves. Of the 90 receptors the majority of the afferents were found in the recurrent cardiac nerve. The right stellate cardiac nerve contained afferents only from the right atrium. The craniovagal and caudovagal nerves contained afferents whose cardiac receptors were located primarily in the right atrium and right ventricle; the recurrent cardiac nerve had afferent fibers from ventricular receptors located in both chambers. Note that the recurrent cardiac contained a few chemosensitive receptors.

TABLE I

RIGHT THORACIC AUTONOMIC NERVES

RECEPTOR	STELLATE CARDIAC	RECURRENT CARDIAC	CRANIO-VAGAL	CAUDO-VAGAL	TOTAL
S.A. Node	3				3
Right Atrium	4	3		5	12
Right Ventricle		21	4	7	32
Anterior Papillary Muscle		13	3	3	19
Total Upper Ventricular Septum		1			1
Left Ventricle		3			3
Aortic Root		8			8
Pulmonary Inflation		2	2	2	6
Pulmonary Deflation		2			2
Chemoreceptor		4			4
TOTAL (n=20)	7	57	9	17	90

Table I represents locations of those thoracic receptors located in twenty dogs, as well as the nerves in which each receptor had its afferent input. Note that the right stellate cardiac nerve was found to contain only right atrial receptor traffic, whereas the caudal vagal and craniovagal nerves had afferent traffic only from the right side of the heart, the recurrent cardiac contained afferent nerves from receptors in the right atrium, either ventricle, and the aortic root.

Table II summarizes the location and type of receptors whose afferents were in the left thoracic autonomic nerves. The left stellate cardiac nerve contains, with one exception, nerves from atrial receptors. The predominant afferent traffic in the ventromedial and dorsal nerves from aortic receptors; the ventrolateral nerve was virtually devoid of afferent activity and chemoreceptor afferents were located primarily in the innominate nerve.

Table III represents the data obtained from all thirty-two experiments in which the receptors are categorized (and compared on a percentage basis) according to their location and behavior. Over 50% of the receptors were located in the aorta and 25% were in the ventricles. Almost 5% of the receptors were chemosensitive.

TABLE II

LEFT THORACIC AUTONOMIC NERVES

RECEPTOR	STELLATE CARDIAC	INNOMINATE	VENTRO-MEDIAL	DORSAL	LATERAL	TOTAL
Right Atrium		2				2
Left Atrium	32	4	7		1	44
Right Ventricle		4				4
Left Ventricle	1	39	15			55
Pulmonary Artery			2			2
Aorta		19	114	95		228
Pulmonary Inflation			2			2
Pulmonary Deflation		10				10
Chemoreceptor		10	4	2		16
TOTAL (n=12)	33	88	144	97	1	363

The location of receptors (left column) and the left thoracic autonomic nerves in which the afferents of these receptors course (upper line) are compared for the 363 receptors located in twelve dogs. Note that the left stellate cardiac nerve contained primarily atrial receptor afferents and that the dorsal cardiac nerve primarily aortic receptor afferents. Chemosensitive receptors had afferents primarily in the innominate or ventromedial nerves.

TABLE III

TOTAL RECEPTOR LOCATIONS

RECEPTOR	NUMBER	PERCENT OF TOTAL
S.A. Node	3	0.6
Right Atrium	14	3.2
Left Atrium	44	9.7
Right Ventricle	55	12.1
Left Ventricle	58	12.8
Bilateral Ventricle	1	0.2
Pulmonary Artery	1	0.2
Aorta	236	52.4
Pulmonary Inflation	8	1.8
Pulmonary Deflation	12	2.6
Chemoreceptor	20	4.4
TOTAL (n=32)	453	100.0

Summary data of all the thoracic receptors located in the thirty-two experiments listed as to location and type of receptor as well as a percentage of the total for each anatomic type of receptor. Note that over fifty percent of all the receptors were located in the aorta.

CHAPTER V

DISCUSSION

Cardiac receptors have been assigned a minor role in conventional concepts of heart function, despite the fact that there has been ample evidence for mechanoreceptors in the atria (9, 23, 31, 70, 93, 95). However, anatomical identification and function of cardiac receptors have been scanty at best (24) and in fact physiologically active receptors in the ventricles have never been documented. The characteristics of the mechanoreceptors and chemoreceptors located within specific regions of the heart will be analysed separately, their differences elucidated, and finally concepts of possible receptor interaction will be discussed.

A. Mechanoreceptors

1. Atrial Receptors

All the cardiovascular mechanoreceptors identified in this study were characterized by neural activity which was related to the cardiac cycle; that is each

mechanoreceptor activity had a maximum and minimum firing pattern which was repetitive and synchronous with each cardiac cycle and silent during cardiac standstill or fibrillation. Thus cardiac mechanoreceptors could easily be distinguished from pulmonary mechanoreceptors, the only other type of phasically-active receptor found. Further identification was facilitated by the fact that mechanoreceptors from the atrium and great vessels had afferent nerve traffic with action potential spikes which were of longer duration (0.65 to 1.35 milliseconds) than ventricular receptor afferent impulses (0.25 to 0.55 milliseconds); receptor location was easily performed in the atria and aorta by direct, local distortion of the receptor. Atrial receptor impulses recorded from afferent nerves showed action potential durations of 0.65 milliseconds to 1.10 milliseconds; the conduction velocity of atrial receptor afferent nerves was 10-13 meters per second, placing them in the A^{γ} or $^{\delta}$/III category (designated AIII) of neural fibers (88). The maximal atrial receptor firing frequencies were found to be 260 per second for right atrial receptors and 120 per second for left atrial receptors. Left atrial receptors were localized primarily around the pulmonary vein orifices and posterior atrial wall had receptor

fields covering over a square centimeter in size, while those of the right atrium were located not only posteriorly near the lateral aspect of the pulmonary veins and arteries but also on the right lateral surface and particularly near the roots of the vena cava. Some receptors were located on the ventral superior vena cava up to four centimeters from the superior vena cava - atrial junction. The right atrial receptors, particularly those concentrated within the sinoatrial node region (53, 69) (Figure 21), covered a much smaller zone of tissue than the left atrial receptors; these receptors responded to distortion of an area as little as a millimeter or less in diameter. Atrial receptors are so sensitive to local distortion that they were activated maximally by gentle blowing or touch with a hair.

Since the first postulation of sinoatrial nodal receptors (36), experimental evidence of their existence has been conjectural (21) despite histological proof of this region's high level of innervation (17, 53). Not only are there numerous length receptors within the sinoatrial node (Figure 1, Table I) but they appear to be highly sensitive and localized. They responded, as did all atrial receptors, to distention or shortening of the highly discrete regions of the

receptor field; high firing rates of these receptors was easily achieved with minimal tissue distortion. When local atrial tissue was relatively quiescent (i.e. fibrillation or standstill) these receptors ceased firing. Not only were they activated by gently blowing on the epicardium, but when the atrium was sectioned from the heart it was found that epicardial and not endocardial distortion initiated activity. Histological examination of these highly discrete regions of the atrium demonstrated nerves which projected bare nerve endings onto the epicardium, without any specialized structures surrounding these nerves. This finding contravenes the existing opinion in anatomical (59) as well as physiological (23) reports that the neural structures associated with cardiac receptors are small bulges at the terminations of the nerve bunches.

The impulse traffic of each atrial receptor quite varied (Figures 1 and 2), depending on the location of the receptor. Right atrial receptors were not influenced by pulmonary dynamics (respiratory cycle) in contrast to left atrial receptors; the left atrial receptors frequently behaved differently during inspiration and expiration due to the fact that positive pressure inflation of the lungs, not only changed left atrial pressures, but also distorted

the posterior atrial wall in open chest animals (Figure 1, A and B). Atrial receptors frequently had augmented or depressed activity after atrial changes. For instance, upon cessation of atrial distention the activity of a receptor frequently was silenced even though pressures returned to control levels (Figure 2) - a form of receptor adaptation. It appears that this behavior is a function of the tissue surrounding the receptor for there is no adaptation noted with direct distention of mechanoreceptors. Little adaptation was found in the mechanoreceptors of the heart region in response to local distortion; local changes in length (Figure 1, C) were accompanied by immediate receptor activation or deactivation - upon cessation of length changes the receptors immediately returned to control functioning (Figure 1, D). All the atrial receptors were length receptors covering different areas of tissue, as well as different regions of the atria. These two factors were the only ones which could be discerned to account for the specific afferent impulse characteristics noted for receptors in differing regions of the atria.

Paintal (93) described two types of atrial receptors (A and B types) and that classification is in vogue at present (9, 23, 31, 70, 95), to the exclusion of other

possibilities. In fact, Paintal (93) cautioned that the "B" atrial receptors were obscure and might in fact be the same as "A" receptors. In the present series of experiments no such differentiation was noted; there was no group of receptors which consistently fired in relationship to atrial systole or diastole (9) - some receptors fired twice per cardiac cycle (Figure 1, A). Of the sixty-one atrial receptors identified, all were sensitive to length changes within the wall of the atria; these local changes were presumably determined by local muscle contraction and atrial pressures, as well as extra-cardiac mechanical events (respiratory motion as well as alterations in pulmonary vein pressure). Thus the atrial receptors generated specific afferent traffic that reflected complex interactions of these mechanical events; left atrial receptors were particularly effected by respiratory mechanics in the open chest preparations.

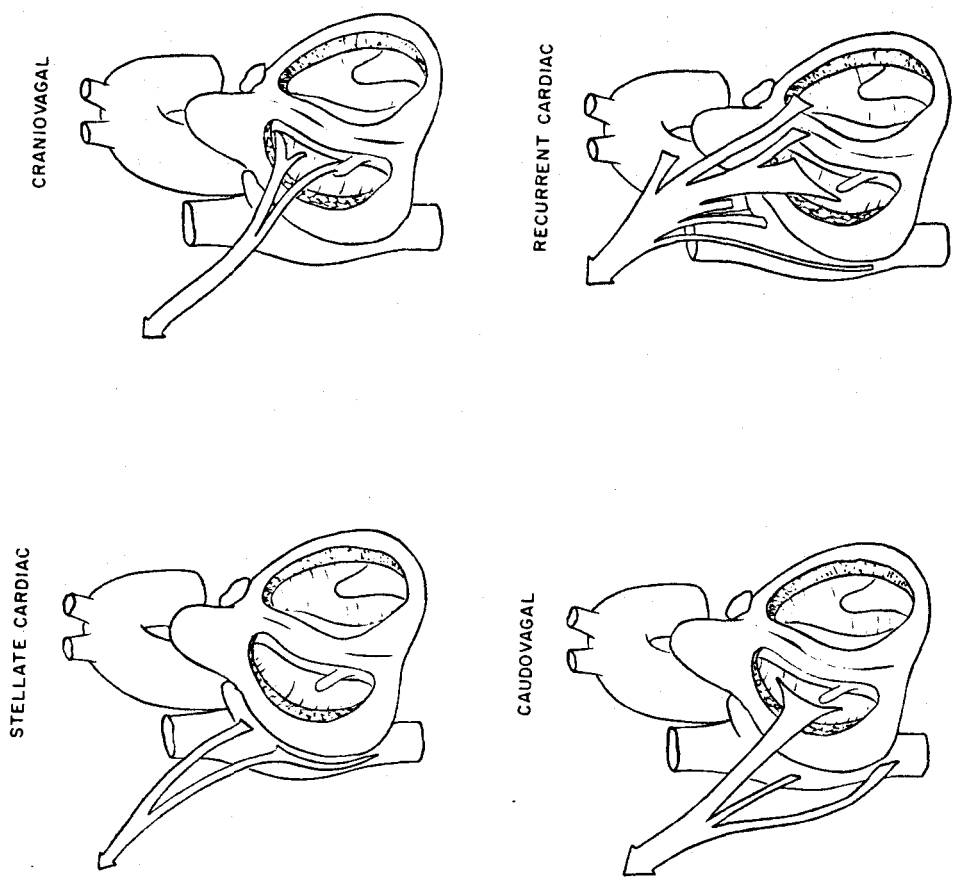
The afferent nerves from atrial receptors coursed in specific thoracic nerves - the right stellate cardiac, recurrent cardiac, caudovagal, and innominate nerves for right atrial receptors and the left stellate cardiac, innominate, ventromedial and the ventrolateral nerves for left atrial receptors (80, 83, 84). Since the

realization that there are discrete autonomic nerves innervating the heart (58), evidence has accumulated demonstrating that specific thoracic autonomic nerves have very specific chronotropic and inotropic effects (106). Thus, it is of more than passing interest that the right stellate cardiac nerve is known to have its efferent projection specifically to the sinoatrial node (106), for most of its afferent nerves come from receptors located in or around this node (Figure 19, Table I). Also, most of the left atrial receptors have afferent fibers in the left stellate cardiac nerve, a nerve to date considered to have no cardiovascular function because of its negligible efferent activity (106). Thus specific nerves are shown here to carry either or both afferent and efferent nerves associated with atrial function.

Atrial receptors are primarily clustered near the orifices of the vena cava and pulmonary vessels and they are sensitive to length changes in regions of tissue of differing area. Receptors in the superior vena cava or S.A. node were localized in small zones; those in the posterior atria and in particular in the left atrium occupied an area equal to a square centimeter or more of tissue. Atrial receptors are capable of a great range of afferent nerve activity during normal

FIGURE 19

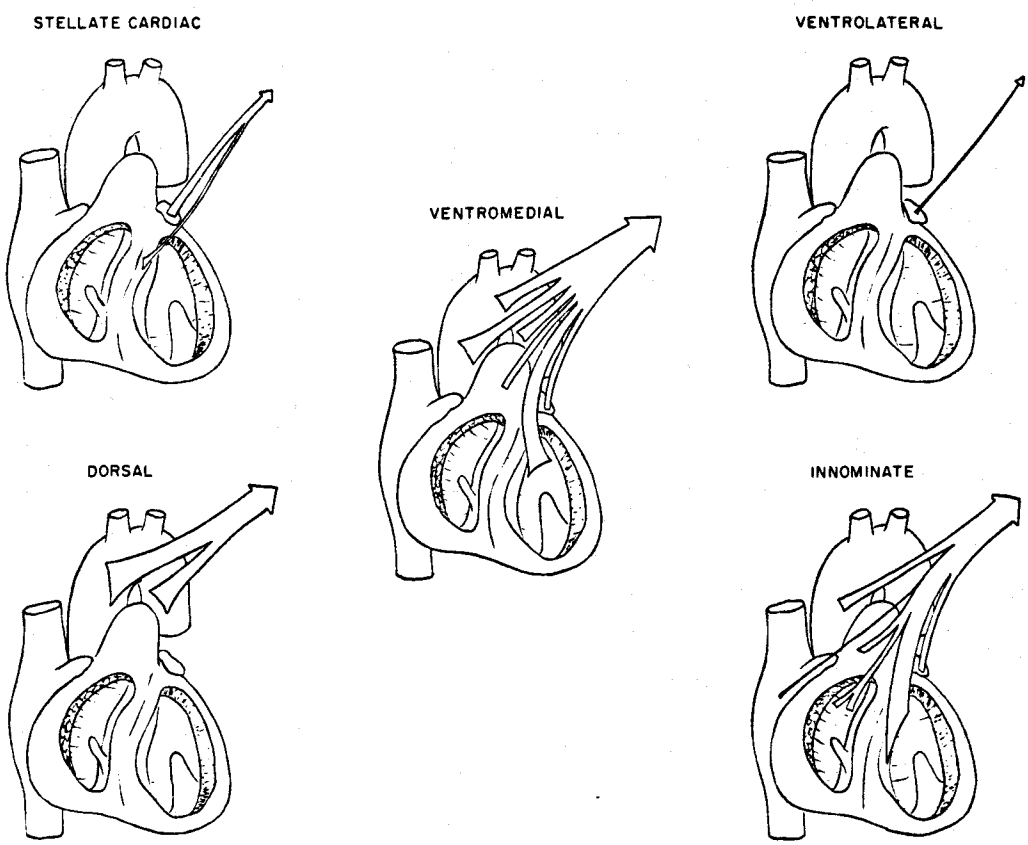
LOCATION OF RECEPTORS WITH AFFERENTS IN THE RIGHT THORACIC NERVES



This schematic representation of the four major thoracic autonomic nerves which arise from the cardiovascular region denotes the location of the receptors which have afferents in each nerve. The afferent stellate cardiac arises only from atrial receptors whereas the craniovagal was found to have only ventricular efferents. The recurrent cardiac had afferents from atrial, ventricular, as well as aortic receptors.

FIGURE 20

LOCATION OF RECEPTORS WITH AFFERENTS IN THE LEFT THORACIC NERVES



The afferent pathways from specific cardiovascular receptors in the left thoracic autonomic nerves d onstrates that specific left-sided nerves contain afferents from specific regions. Note in particular that the left stellate cardiac nerve contained mostly afferents from the left atrium, whereas the dorsal nerve had only aortic receptor afferents. The innominate and ventromedial nerves contained atrial, ventricular and aortic fibers. It is of interest to note that the ventrolateral nerve, an active efferent nerve, contained few afferents.

myocardial dynamics due to this variety of location and size of receptor field. When the atria are emptied (i.e. via occlusion of the vena cava) their activity ceases, and conversely when the atria are distended their activity augmented. However this behavior is not found for all atrial receptors as a few left atrial receptors decreased afferent activity on atrial distention, presumably due to the fact that atrial contraction is minimized and thus does not change receptor length significantly. The fact that such a variety of afferent activity occurs when the atria are subject to dynamic changes serves to demonstrate the lack of knowledge concerning how these length receptors are coupled to the atrial wall.

Peripheral nerves have been classified by their physiological activity (71) as well as by their histologically demonstrated diameters, rate of impulse conduction, spike duration, and other properties (89). The two stellate cardiac nerves, which contain afferent nerves arising primarily from the atria, have numerous medullated fibers; the left stellate cardiac nerve, which has little efferent chronotropic, tonotropic, or inotropic cardiac function but which contains numerous afferent fibers, was found histologically to have over 70% of its axons medullated with diameters of the myelinated

nerve fibers from 2.0 to 3.8 microns, a few fibers being up to 5.2 microns in diameter. The action potential duration of afferents in this nerve were from 0.65 to 1.10 milliseconds and the afferent nerve conduction velocities ranged from 10 to 13 meters per second. Thus these can be classified (88) as A/III class fibers. The duration of the action potentials of atrial receptor afferent impulse have similar characteristics to aortic, pulmonary artery, and pulmonary tissue length receptors, as well as chemoreceptors, but different from ventricular receptor afferents.

Atrial receptors are thus evidently length sensitive and their afferent traffic determined by all the interactions effecting contraction of local segments of the atrium. Alterations of local contractility (i.e. inotropic augmentation via norepinephrine) change receptor activity and thus their activity reflects sensitively minor as well as major fluctuations of atrial dynamics.

2. Ventricular Receptors

Due to the relative inaccessibility of mammalian ventricular receptors, most of them being endocardial or deep within the myocardium, their characterization is difficult. This in part accounts for necessity of unphysiological procedures - i.e. chemical stimulation or

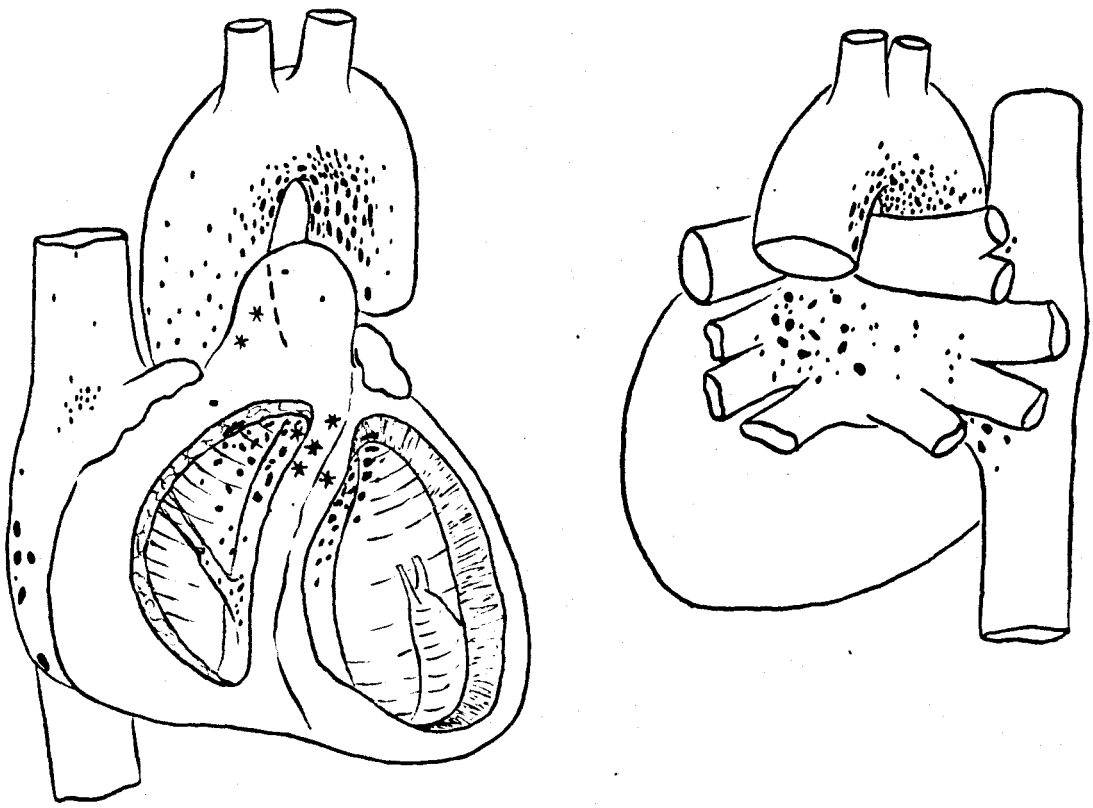
physical distortion - for their elucidation (86, 94, 126). A report by Coleridge et al (26) demonstrated beyond question functioning receptors in the ventricles; they described two types of receptors - one functionally related to the cardiac cycle and located in the endocardium and myocardium, the other having irregular and sparce discharges not related to the cardiac cycle and being located epicardially. However in their study, as in most studies concerning cardiac receptors (26, 28, 93, 94, 119), drugs were found necessary in order to induce the afferent traffic - capsaicin, nicotine, and veratrine. It is very difficult at present to adequately assess the role of these agents; but it is evident that cardiac mechanoreceptors which are non-functioning will become evident only after these drugs are used. Frequently in the present series of experiments cyanide infusion activated cardiac mechanoreceptors which were previously silent (Figure 16, panels 4 to 6); these receptors were active only when the ventricular pressure was augmented following the drug infusion. Thus there are probably many more mechanoreceptors which this present study did not discern due to the fact that chemicals were not employed; the physiological role of receptors which can only be elicited by such chemical stimulation was not

considered, due to the fact that such chemicals alter cardiodynamics greatly.

The characteristics of ventricular receptors differ greatly from those found in the atria or great vessels. These receptors are most frequently active during the development and at the peak of ventricular pressure - although in control conditions a few ventricular receptors are active in diastole as well. Whilst fourteen percent of all the cardiovascular receptors were found to be atrial, over twenty-six percent arose in the ventricles (Table III); the ventricles have a great number of length receptors which are located primarily in the endocardium or deep myocardium of the outflow regions (Figure 21). The receptors were found to cover endocardial areas of 0.5 cm^2 to over 9 cm^2 and all responded to minimal local length changes (i.e. touch or blowing upon exposed endocardium) (Figures 9, 11, and 12). Ventricular receptors had afferent nerve traffic with action potentials of relatively short duration - 0.25 to 0.55 milliseconds; these nerves have conduction velocities of 0.9 to 1.4 meters per second as well as a maximum firing frequency of 200 impulses per second. Histologically these small myelinated nerves were found to be 0.8 to 1.1 microns in diameter so that their fibers may be

FIGURE 21

DISTRIBUTION OF LENGTH AND CHEMOSENSITIVE RECEPTORS FOUND IN THE HEART AND GREAT VESSELS



A composite schematic representation of the anterior and ventricular endocardial surfaces (left side of Figure) as well as posterior surfaces (right side of Figure) of the heart demonstrates the location and approximate size of length sensitive (solid one) and chemosensitive (asterisk) cardiovascular receptors. Note the concentration of length receptors in the S.A. node, posterior atria, outflow tracts of the ventricles, as well as the arch of the aorta. The chemoreceptors were located in the ventricular septum and medial aortic root.

classified as belonging to the C group (89). Their short action potential duration and spike amplitudes make these afferent impulses difficult to record (Figure 4), particularly with the great loss of definition which occurs when taping the information. The maximum firing rate obtained by local distortion of ventricular receptors (Figure 12) reaches 200 impulses per second - a frequency comparable to maximum frequencies reached for aortic receptors, but considerably below that of atrial receptors. The fact that ventricular receptor afferents were all C fibers is of particular interest in view of the fact that ventricular nerve fibers examined by electronmicroscopy belong only to the C class (44). Microscopic analysis cannot determine if a fiber is afferent or efferent; however as ventricular receptor afferents had been physiologically identified as C class fibers and microscopically only C fibers have been reported in the ventricles, confirmation of anatomical and physiological interdependence is exemplified.

The characteristics of ventricular receptors are varied, depending upon the location and zone of tissue influenced by the receptors; most are confined to a zone of tissue which functions in a uniform fashion. With the exception of one receptor (Figure 11), all 114

ventricular receptors were silent during diastole in control states. Incising the pericardium and the concomitant diastolic enlargement of heart size was accompanied by an increase in the traffic of ventricular receptors; it is worth noting that all physiological interventions were done when the pericardium was opened. Right and left ventricular receptor traffic with few exceptions (Figure 7) occurred in the S-T segment period of a standard reference electrocardiogram (Figures 8 and 9). Right ventricular receptors responded to physiological interventions which altered right ventricular function, although being influenced by left ventricular dynamics. On the other hand, left ventricular receptors responded only to changes in left chamber pressures (Figure 10). This is in complete accord with studies conducted on bilateral ventricular septal force generation (8), as well as other regions of the heart (4, 6); separate regions of the heart are known to behave differently under physiological conditions (41, 47, 57, 103, 112, 113, 115) - the right and left ventricles commence contracting at differing times (57) and each chamber contracting asynchronously (47, 103). Thus there is good support for the concept that differing anatomical regions of the heart (4) have separate contractile characteristics;

this is most evident in the right ventricle and in particular with regard to the papillary muscles of that chamber (6). The afferent traffic from ventricular receptors exhibited these regional functional characteristics; right ventricular receptors were augmented by pulmonary artery occlusion (Figure 3, D; Figure 4) and depressed during vena cava inflow occlusion (Figure 4, E; Figure 6). When the force of contraction was augmented, receptors in either ventricle increased their firing (Figure 4, F and G; Figure 10); during isoproterenol augmentation the burst of afferent impulses was confined to systole, whereas following norepinephrine the nerve traffic was increased so that it was continuous throughout systole and diastole, being maximal in systole (Figure 4). These length receptors are sensitive to diastolic tone in control states and particularly during the influence of norepinephrine. This is an important point, as yet unresolved, as diastolic tone may be a key determinant of cardiac function (49, 108). Subsequent to early analysis of the cardiac effects of catecholamines (34, 35, 91) the inotropic and chronotropic effects of these agents have been elucidated (105). Norepinephrine effects the peripheral vascular resistance more than isoproterenol, the former agent augmenting systemic diastolic pressure to

a greater extent than isoproterenol (8). While the mechanisms of cardiac augmentation are not clear, the peripheral vascular resistance changes presumably effect diastolic cardiac tone and this may account for the differences in diastolic receptor activity during varying positive inotropic states. The increased peripheral vascular resistance, by increasing the afterload, may increase end-diastolic volume; this would tend to cause receptor lengthening and thus may account for the receptor activity during diastole. During norepinephrine augmentation there is an increase in diastolic ventricular tone (4) and thus receptor is activated throughout diastole as well as systole (Figure 4, panel G). It is evident that the ventricular receptors are a very sensitive monitor of diastolic tone and are continually altered throughout each cardiac cycle.

The right ventricular papillary muscle region appears to have a number of receptors (Figure 21); the majority of these receptors were found to spread onto the adjacent septum. These receptors were found to either decrease or increase afferent traffic when the papillary muscle-chorda complex was distended (Figures 4 and 6). On one occasion the distention of the papillary muscle caused not only increased traffic, but the initial

impulses to begin earlier in the cardiac cycle (Figure 7) - a striking example of the fact that not only the impulse number, frequency and total duration of activity are important but also the alteration in the onset time of impulses in relationship to the cardiac cycle. Each receptor was activated by local distortion and thus the afferent traffic of these receptors is considered to be related to the anatomic arrangement they had within the myocardium. Severance of the cervical vagi, with concomitant augmentation in myocardial force and heart rate, grossly altered receptor afferent traffic which increased in accord with the increase local force changes. The vagi are known to innervate the ventricles (109) effecting their contractile state (4) and with the removal of their influence local contractility and thus ventricular receptor activity was augmented. Lidocaine, a local anesthetic drug known to change the properties of cardiac cells (7, 78), when infused as a bolus into the root of the aorta did not effect the receptor - afferent nerve mechanisms. Right ventricular papillary muscle distention is known to initiate arrhythmias (6) which are under neural influence. As many arrhythmias are of neural origin (7) and can be diminished by Lidocaine, this drug has been thought to effect afferent nerve activity (7).

However, as cardiac length receptors are not sensitive to Lidocaine or hypoxemia, the anti-arrhythmic effect of this drug is probably not related to afferent neuronal mechanisms.

The interventricular septum is frequently thought of as being confined to the left ventricle - anatomically (73, 111) and functionally (50, 113). However, it is increasingly clear that the septum can be divided functionally into right and left portions (8). This regional functional behavior was demonstrated by Walton-Brodie strain gauge arches placed in varying endocardial and epicardial regions; these devices demonstrate accurately local behavior (110). Left ventricular septal contractility was augmented during aortic occlusion but was unaffected by pulmonary artery occlusion; on the other hand the right ventricular septum was augmented by both pulmonary artery and aortic occlusion - presumably because the bulky left septum directly affects the right septal dynamics. This functional differentiation was noted also when analysing ventricular septal length receptors. Left septal receptors responded by increasing their afferent traffic when the aorta, but not the pulmonary artery, was occluded (Figure 10). Right ventricular septal receptors initiated a great increase of

traffic with pulmonary artery occlusion but minimal increases with aortic occlusion. A fascinating addendum to these observations is the fact that some receptors were sensitive to both right and left septal dynamics (Figure 12); the activity of these receptors was augmented almost equally by pulmonary artery or aortic root occlusion. Upon cardiac fibrillation ventricular length receptors were inactivated; it was found by direct probing that these receptors were located primarily on the endocardial outflow tracts of both ventricles, particularly on the upper septum (Figure 21). A few receptors were deep in the ventricular muscle and these were not sensitive to endocardial distortion; only one receptor was located on the epicardium. This is contrary to the view that ventricular receptors are located in or near the epicardium (118).

When ventricular premature contractions occur (Figures 8 and 10) afferent traffic from ventricular receptors diminish significantly; this is probably due to the poorly developed contraction that occurs in conjunction with ventricular ectopic rhythms which would cause lessened local changes around the receptor. Thus there is a myriad of receptor patterns which can occur during each contraction and these are determined by region of

tissue covered as well as their anatomical location and function of local muscle segment systole and diastole. One can only speculate as to the variety of information received by the autonomic nervous system from all the ventricular receptors. One region of the right heart can be distended and thus effect contractility in the rest of that chamber to increase on the next beat, as well as presumably augment the left ventricle in preparation for the increased filling volume it will receive; numerous interaction can thus occur. The majority of right ventricular receptors have afferents in the recurrent cardiac nerve and the afferents from left ventricular receptors in the innominate nerve (Tables I and II). Systemic injection of propanolol, phentolamine, lidocaine, or procaine did not block the afferent traffic of the cardiac receptors.

3. Major Vessel Receptors

Of all the cardiovascular receptors 54.8% were from the major vessels - since there was only a few located in the superior vena cava and one on the ventral pulmonary artery, the vast majority were aortic; of the four hundred and fifty-three receptors located, two hundred and thirty-six were aortic - a striking finding that so many receptors were located in the ascending

and arch regions of the aorta (Figure 21). Baroreceptors have been located in the carotid sinus region (18, 19, 63, 64) with receptor afferent nerve activity responding to vascular absolute pressures ranging from 40 to 200 mm Hg. Baroreceptor mechanisms have been considered to exist in the innominate artery - aorta zone (86), although their presence in that region has been doubted (27).

The aortic receptors were confined to the adventitia and outer media of the vessel; sectioning of the media with a scalpel from these outer layers did not disrupt receptor function and gently blowing over the region of a receptor initiated its firing, making it unlikely that they are located deep in the media. Upon histological examination neural elements were found only in the adventitia of the vessel. This is in accord with recent reports on carotid sinus baroreceptors (32). The receptors which are located in the first centimeter of the aorta cover very small areas of tissue (up to one millimeter square); aortic receptors cover larger zones of tissue as one progresses to the arch and finally to the descending aorta where a receptor may cover a one centimeter by two centimeter elipse of tissue. These receptors respond instantaneously to length changes (Figure 15) as do other cardiovascular receptors and demonstrate no gross

local adaptation; when they are distorted with increasing weights their traffic increases to an average maximum of 200 impulses per second without any change in frequency once the load has been applied. Upon termination of the local distortion they instantaneously return to control firing levels (Figure 15, panel E). An impulse initiated from aortic receptors is characterized by a duration of .70 to 1.35 milliseconds, most of them being within the range of 0.75 to 1.25 milliseconds. Histological examination of the dorsal cardiac nerve which contains primarily aortic afferents, with few if any efferents (106), reveals fibers with diameters of 1.6 to 2.3 microns; the maximum firing frequency of aortic receptors was 200 impulses per second and the conduction velocity of their afferents was from 10 to 16 meters per second; thus the aortic receptor afferents can be calssed as a group A/III fibers (88). The aortic receptor afferents in the recurrent cardiac nerve arose from receptors located only in the first centimeter of the aortic root, while those in the left thoracic nerves arose from the whole arch - the innominate aortic nerve afferents arising primarily from receptors in the ascending aorts. It is of great interest that one nerve (dorsal cardiac) contains afferents almost exclusively from the aorta and

anatomically it is found to terminate in that location.

Although there is some variability in behavior of aortic receptors, the two depicted in Figures 14 and 15 are typical of the majority; occasionally aortic receptors in control states fired throughout systole and diastole and others fired only one or two impulses per total cycle. However generally they fired maximally as peak aortic pressure was achieved, were silent during the dicrotic notch period, and fired again minimally during diastole. The impulse traffic from a single afferent could easily be increased or decreased by alterations of aortic pressure. When the pressure was reduced in the region of a receptor the traffic was diminished or absent; when local pressure was augmented the receptor traffic also increased (Figure 14). The maximal firing rate was achieved during the development of peak pressure (Figure 14, panel C) but not at the instant of peak pressure. When dP/dt was great the traffic was also greater than during systoles with lesser dP/dt even though the same peak pressure was achieved (compare panels C and E of Figure 14); thus the aortic length receptors are sensitive to rate of change of pressure as well as peak pressure. Aortic receptors display no adaptation to local stretch for local stretching (Figure 15)

of aortic receptors initiated immediate firing at fixed rates, which returned to control rates immediately upon cessation of the stretch; vessel wall arrangement is such that adaptation occurs for the total mechanism only. This might entail a readjustment of receptor adventitial interactions or the influence of the autonomic nerves altering vessel wall tone. The aortic receptors which covered a large area of tissue often fired almost continuously when the aortic pressure was increased. Different aortic receptors responded differently to comparable pressure changes; in some instances a minimal increase of aortic pressure generated a maximal increase in receptor traffic (Figure 15), while considerable aortic pressure raises were necessary to activate other receptors to maximum levels (Figure 14). Aortic receptors span a range of location, receptor area size, as well as aortic interactions. When a whole nerve containing a great number of aortic receptors is analysed, synchronous activity is very evident (Figure 13). It is remarkable indeed that every dorsal cardiac nerve, as well as at least one major division of the ventromedial nerve, contains so many aortic afferents that whole nerve activity is easily recorded.

The whole nerve preparation exhibits three or four "waves" of afferent activity during control cardiac cycles.

The three major "waves" are correlated with the systolic pressure, the dicrotic notch pressure, and the diastolic phase; frequently a fourth "wave" was evident (panel B, Figure 13) which preceded systole and was made very evident during bradycardia (panel C, Figure 13). These findings are interesting when compared with the knowledge that three (3) and even four (79) distinct pressure waves occur in the origin of the descending aorta. Local aortic longitudinal and radial measurements (96, 97) have conclusively demonstrated that the wall of the aorta undergoes up to three local length changes per systole (98); it appears that the myriad of aortic receptors are monitoring local aortic arch length changes including three and sometimes four per cycle. These alterations in circumferential and longitudinal length are very evident during bradycardia presumably due to the fact that reflected pressure waves interact with the ejected blood (79) over a longer period of time. During bradycardia the four waves of afferent nerve activity were very evident (panel C, Figure 13). Some activity begins before the aortic valve presumably is open and may arise from ventricular receptors or aortic receptors distorted by the ventricular systole. With augmentation of pressure the individual aortic receptors increase their activity

and thus a whole nerve preparation may demonstrate continuous traffic with maximal activity during systole (D, Figure 13). Even during post-vagotomy tachycardia the four waves of afferent impulses were shortened but remained very evident (E, Figure 13). Thus aortic receptors are very numerous and responsive to local aortic pressure changes. As with cardiac receptors they are modified by local events which cannot be measured utilizing conventional physiological techniques [i.e. Patel and Fry (98) only recorded three aortic wall length changes per systole]. This great aggregate of receptors monitoring the root of the major vessel directing blood from the heart to the body must be of great physiological importance. This is a very active and sensitive mechanism for measurement of the central blood pressure; however, if that was all that was necessary, surely only a few receptors would suffice. The receptors lining the entire ascending aorta and aortic arch must measure more than peak pressure and rate of development of pressure - the pressure waves as they proceed down the aorta and are reflected back towards the heart probably activate aortic mechanoreceptors along the aorta in a variety of ways thus presumably sending afferent traffic that will be decoded centrally to assess the total aortic pressure

and flow dynamics.

4. Pulmonary Receptors

The pulmonary receptors are included in this study to exemplify their similarity to the cardiovascular length receptors. At the outset of the experiments, when the nerves were not dissected down to the heart, there were many inflation or deflation receptor afferents found in the thoracic cardiac nerves. These afferents have action potentials of long duration (0.90 to 1.30 milliseconds) and rhythmic activity related to the positive pressure respiratory cycle. They were responsive not only to respiratory rate but also the rate of respiratory inflation (Figure 16) or deflation. When localized, generally in the hilus region or nearby pulmonary tissue, all these receptors responded in a similar fashion as cardiac receptors to length changes. It appears that the function of these pulmonary receptors is determined by their anatomic arrangement to pulmonary tissue for the length sensitive receptors, all of which responded to local tissue distention, can function as either inflation or deflation receptors, they also demonstrated no adaptation on local distortion. Thus length receptors, similar to those found in the heart and great vessels, are located in the hilar regions of the lungs.

B. Chemoreceptors

Twenty chemosensitive receptors which had afferents coursing in the thoracic autonomic nerves were identified - 4.6 percent of the cardiovascular receptors and 4.4 percent of all thoracic receptors found (Table III). The afferent traffic from chemoreceptors was different from all the length receptors: 1) chemosensitive receptors had continuous non-cycling afferent nerve activity, unrelated to the cardiac cycle; 2) chemoreceptors were uneffected by local tissue dynamics either during systole or during direct tissue distortion in the receptor field; 3) chemoreceptor traffic was augmented by periods of hypoxia or in the case of ventricular chemoreceptors, periods of coronary artery occlusion or cyanide infusion; 4) following cardiac fibrillation mechanoreceptors were inactive while chemoreceptor traffic increased. Cardiovascular chemoreceptors have been located histologically (29) and physiologically (37, 38, 39, 88). Although chemoreceptors have been postulated to be in the heart (28) there has been no conclusive proof for such a concept until recently (41) when perfusion of chemicals into coronary arteries gave strong credence to this thesis. In the present study surgical isolation of tissue in which chemosensitive receptors were located was found to be the

most expedient method of precise receptor location; the chemoreceptors were found to be concentrated in the cranial mid-septum (where there are few mechanoreceptors) or the medial aspect of the aortic root (first centimeter, Figure 21, asterisk). This does not in any way preclude other chemosensitive receptors being located elsewhere in the heart and great vessels, but to date this is the only definitive localization of such receptors in the ventricle or aortic root. It was the septal chemoreceptors which respond to occlusion of the coronary artery perfusing its region; occlusion of coronaries not perfusing the region of a receptor did not effect its activity.

The chemosensitive receptors fired continuously during control experimental states at a rate of between 30 and 80 impulses per second. The carotid body chemoreceptor resting firing rate has been reported to vary from 14 to 50 impulses per second, a range somewhat lower than the cardiac chemoreceptors (37, 38). Chemoreceptor afferent action potential duration were from 0.60 to 1.20 milliseconds duration and the conduction velocities of the afferent nerves tested were 9 and 12 meters per second respectively; thus chemoreceptor afferent fibers belong to the A/III class of fibers. During

periods of hypoxia the chemoreceptor traffic increased to 56 - 140 impulses per second and following chemical stimulation (cyanide) the impulse traffic increased to 120 - 160 impulses per second. The maximal chemoreceptor firing rate was considerably below that reached by mechanoreceptors, particularly those from the right atrium; however, due to the fact that chemoreceptor traffic was continuous, the number of impulses delivered centrally over a period of time was greatest for maximally stimulated chemoreceptors. This flood of afferent traffic must effect considerably the central mechanisms and may be sensed as maximum organ activity - pain. The massive output of afferent traffic from a stimulated chemoreceptor may dominate all cardiac afferent traffic. The chemosensitive receptors responded rapidly to cyanide infusion into the aortic root receptors (i.e. lag time of 2-4 seconds). When respiration ceased or a major vessel supplying the chemoreceptor was occluded, after about 30 seconds the chemosensitive receptor traffic started to increase and after a couple of minutes was considerably elevated. It is important to note that mechanoreceptors are unaffected by bouts of hypoxia, other than the incidental results of bradycardia and augmented force that developed as a result of the hypoxia; on the other hand chemicals like

cyanide augment ventricular force and mechanoreceptors which were silent then become very active (panel 5, Figure 16). The mandatory use of stimulating drugs by other authors in order to stimulate cardiac receptors presents a major problem in assessing the physiological role of cardiac receptors (23, 24, 31, 93, 94) - a major obstacle when considering the physiological role of reported cardiac receptors. Chemical agents may augment cardiac contraction coincident with the bradycardia and resultant forceful contraction may affect length receptors which were previously quiescent. Cardiac chemoreceptors had afferent nerves in the recurrent cardiac, innominate, as well as ventromedial and dorsal cardiac nerves, the innominate nerve containing most of them. On a number of occasions one nerve bundle, a separate nerve just laterally to the innominate nerve, was found to contain only cardiac chemoreceptor afferents - a specific (cardiovascular) chemoreceptor nerve. Chemoreceptors were the only receptors which continued to fire during ventricular fibrillation (Figure 18), unless the heart underwent external mechanical disruption (Figure 9, 11, and 12). This neural activity gradually increased as the duration of fibrillation was extended (Figure 18) and the receptors continued to fire up to 30 minutes after the

beginning of fibrillation.

Thus, for the first time, cardiac receptors have been reported which are sensitive to hypoxia and/or hypercapnea - local (i.e. coronary occlusion) or generalized. These receptors, located at the aortic root and septal base, are not numerous but are capable of rapid and continuous firing; they are not affected by Lidocaine or atropine, hexamethonium, or propranolol. They presumably monitor the chemical milieu of the heart constantly. As such their role is important in total cardiac function and presumably represent the mechanism whereby the gas tensions of the myocardium as well as aortic blood are monitored - thus the blood gases of the heart tissue or ventricular vasculature and aortic root arterial blood, as apposed to receptors in the carotid arteries, are constantly being analysed.

C. Interactions of Receptors

The description of cardiovascular receptors herein has centered around specific mechanoreceptors, which occur in specific anatomical regions of the heart and great vessels, and cardiovascular chemoreceptors. All of the afferent impulses spread centrally and are presumably integrated at a number of anatomical levels of the autonomic and central nervous systems in order to coordinate cardiac

control via the autonomic efferent nerves. The experimental procedures employed impose gross limitations on the state of the whole animal and in particular its nervous system; chloroform derivatives employed as anesthetics do not grossly depress the autonomic nervous system and in particular the sympathetic ganglionic functions (67). Afferents presumably act upon local ganglia within the autonomic nervous system (65) as well as the central nervous system (96, 101, 105) to alter efferent neural output which in turn regulates the heart; cardio-cardiac reflexes have long been considered (40, 66) and at present evidence is accumulating to support such hypotheses (22, 74, 75, 76). Knowledge of cardiovascular receptors in the heart and great vessels has been paltry and misleading; the present work demonstrates conclusively the presence of a variety of cardiovascular receptors and also gives evidence for the fact that efferent autonomic nerves modulate their activity - a concept adequately demonstrated to function in the carotid sinus baroreceptor mechanism (61). The parasympathetic or sympathetic efferent nervous systems appear to modify cardiac receptor activity, presumably by changing the mechanics of the structures surrounding each particular receptor (Figure 13). There is a remarkable degree of interplay

possible between afferent and efferent systems. The efferent nerves modify the milieu of a receptor which in turn alters its afferent traffic and this in turn is relayed back to the central nervous system. Thus during each cardiac cycle - both diastolic and systolic phases - information is derived from all over the heart, and in particular outflow and inflow tracts as well as the sinoatrial node; this information is integrated and then efferent information related to the various cardiac regions. This allows one to postulate instantaneous control of one cardiac region over its own inotropic, bathmotropic, and dromotropic state as well as other regions of the heart and cardiovascular system or other body functions.

D. Conclusions

Cardiovascular receptors - in particular those located in the heart - although previously described, are generally assumed to play minor roles in cardiac dynamics (70). This same view is often held concerning the efferent autonomic nervous regulation of the heart (70). Reports of the existence of cardiac receptors have been conflicting and sketchy due to the relatively unphysiological conditions employed to reveal them. Atrial receptors, in particular, have been demonstrated

conclusively (11, 93) and a few receptors have been reported to be in the ventricles. Although atrial receptors have been generally divided into two functioning categories (9, 95), this simple grouping was found not to exist - rather, a variety of afferent patterns arose from atrial receptors depending on their location, the zone of tissue covered by a receptor, and the physiological state of the surrounding tissue. They were found to respond to length changes and as such are sensitive to a variety of local atrial wall changes.

Ventricular receptors, sensitive to local length changes, were found to be numerous and dynamically active during relatively physiological conditions. They were located in the endocardium and deeper myocardial layers, only a few being located in or near the epicardium. No chemostimulation was necessary to investigate their function as they were found to be exquisitively sensitive to local length changes; the afferent traffic of the ventricular receptors reflect the local myocardial dynamics of the zone of the receptor. Alterations of contractile patterns of tissue surrounding the receptors via changes in the efferent autonomic nervous system efferent, as well as altered preload and afterload, greated changed their behavior. This thesis demonstrates for the first

time, not only the numerous physiologically active ventricular receptors, but also that efferent nerves can alter the behavior of these ventricular receptors. Right atrial and aortic root receptors were found to respond to dynamic changes in an area of tissue of under a millimeter to about 2 millimeters in diameter. On the other hand, left atrial, ventricular, and descending aorta receptors often extended over areas greater than four square centimeters. Their afferent traffic is modulated by efferent autonomic nerves, for the neuro-chemical milieu of the tissues surrounding a receptor will effect the tissue and thus the activity of the receptor.

Evidence is proffered for the first time to demonstrate the activity of cardiac chemosensitive receptors (66); chemoreceptors were also located in the root of the aorta. These continuously firing receptors are the only ones which spontaneously fired during cardiac standstill or fibrillation and then their impulse traffic increased as the period of cardiac dysfunction increased. The chemoreceptor afferents coursed in four thoracic autonomic nerves, however the majority were located in the innominate nerve (Table I and II); in some animals there was a specific nerve which contained only afferents from these chemoreceptors.

E. Inferences

The concept of specific afferent and efferent autonomic nerves innervating the heart, as well as their interrelationships effecting cardiac function, is just beginning to emerge (106). Highly localized anatomical projections of these nerves has been found to correlate with the great degree of local cardiac control which has been reported (102); the cardiac afferent nervous system is equally discretely organized, with receptors from one area of the heart coursing in specific thoracic nerves (Tables I and II). This localized and sensitive neural system (Appendix I), presumably capable of reflex activity (65, 74), can interact to form cardiac and vascular reflexes. The concept arises of a regulatory system responding rapidly to regional cardiac dynamics and gas tensions throughout systole and diastole; this concept is foreign to prevalent views which consider the sarcomere diastolic length to be the major determining factor of myocardial contractility (117) - the extracardiac mechanisms being superimposed on that major function (117). However, cardio-cardiac reflexes not only explain the possibility of rapid adjustments but also adjustments that occur constantly in highly localized regions of the heart (6). Such neural regulation would effect the chronotropic,

dromotropic, and inotropic states from instant to instant throughout the heart, as well as modulate the diastolic tone of the heart - tonotropism.

No longer can physiologists neglect the role of the autonomic nervous system with respect to internal organs; such regulatory patterns would allow an infinite variety of regulating interactions. Concepts of cardiac function are thus reinforcing those of over a hundred years ago (40) when the mechanical and electrical cardiac events were considered to be under the constant influence of the autonomic nervous system. At each instant throughout the whole cardiac cycle, adjustments of cardiac function are probably occurring; the atria and ventricles are in a constant state of dynamic change being influenced neurally as a result of regional dynamic changes, particularly in the aortic arch. The chemical milieu of the ventricular mass as well as aortic blood also interacts centrally to modulate efferent cardiac control. Cardiocardiac reflexes are probably numerous and constantly changing effecting local and distant regions of the whole system to regulate the ultimate function of the heart - cardiac output.

CHAPTER VI

SUMMARY

Four hundred and fifty-three receptors with afferents in the thoracic autonomic nerves were analysed in thirty-two mongrel dogs in order to determine the dynamic behavior of receptors in and about the heart. Twenty length sensitive pulmonary receptors were located in the hilar regions of the lungs. All the cardiovascular mechanoreceptors had cyclical afferent traffic related to the cardiac cycle, and of these 14.1% were atrial, 26.5% were ventricular, 0.2% were located in the pulmonary artery, and 54.6% were in the aorta; 4.6% of all the cardiovascular receptors had continuous afferent nerve firing and were found to be chemosensitive. The length receptors were located primarily in the sinoatrial node region, the dorsal aspect of the atria, the endocardial outflow tracts of both ventricles, and in the root and innter aspect of the arch of the aorta. Localized regions of the heart and major vessels had receptors with

afferents coursing in specific thoracic nerves - the same thoracic autonomic nerves where the efferent nerves innervating that region have been reported (102). Thus there is a discrete anatomical regional arrangement of the afferent innervation similar to that found for the efferent cardiac innervation.

Atrial and ventricular receptors initiated afferent traffic which was closely related to local cardiac dynamics in the region of the receptors. Ventricular receptors were found to be extremely sensitive to local dynamic events and as such verify previous investigations which measured the regional force generation differences in the various regions of the ventricles and note regional dynamic differences (6, 8, 106). The minute mechanical changes are reflected in altered afferent traffic, however the afferent traffic can also alter over considerable changes such as those found during norepinephrine augmentation. Many aortic receptors were found, and represent by far the preponderant form of thoracic cardiovascular receptor; these numerous receptors apparently monitor outflow dynamics of the left ventricle, presumably represent an extremely important fraction of the afferent input arising from the heart and great vessels. Chemosensitive receptors for

the first time were found to be located in the aortic root and ventricular mass; the latter group responded to periods of coronary artery occlusion and may have an important role in the genesis of coronary ischemic pain.

Thus the heart and the roots of the great vessels have been demonstrated to contain numerous length sensitive receptors which are constantly monitoring local dynamic events. Length receptors in association with chemoreceptors demonstrate that the heart is an organ with numerous physiologically active receptors - constantly in a dynamic state of flux. Knowledge of such a system is important with regard to understanding cardiac contractile behavior as well as its regulation. The heart, with its many functionally discrete regions, is constantly altering local contractile behavior - presumably to maximalize cardiac output in accord to body demands (4, 6, 8). Not only is the circulatory system endowed with functional sensors but also the heart; the heart must be hencewith considered to be an organ with numerous physiologically active receptors. The anatomically discrete afferent nerve - receptor mechanisms and efferent autonomic regional control allows the postulation of highly localized and instantaneously changing modulation of cardiac function via local and central neural reflexes.

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APPENDIX I

The anatomical localization of the thoracic autonomic nerves is important as each nerve has afferent and efferent fibers arising from receptors and going to specific cardiac regions. The terminology of Mizeres (83, 84) has been employed due to its functional simplicity; however, physiological data was not available in the past and the discrete functional arrangement of these nerves not fully understood. Therefore a brief anatomical description of the thoracic autonomic nerves is appended to the thesis in order to clarify the anatomical terms employed.

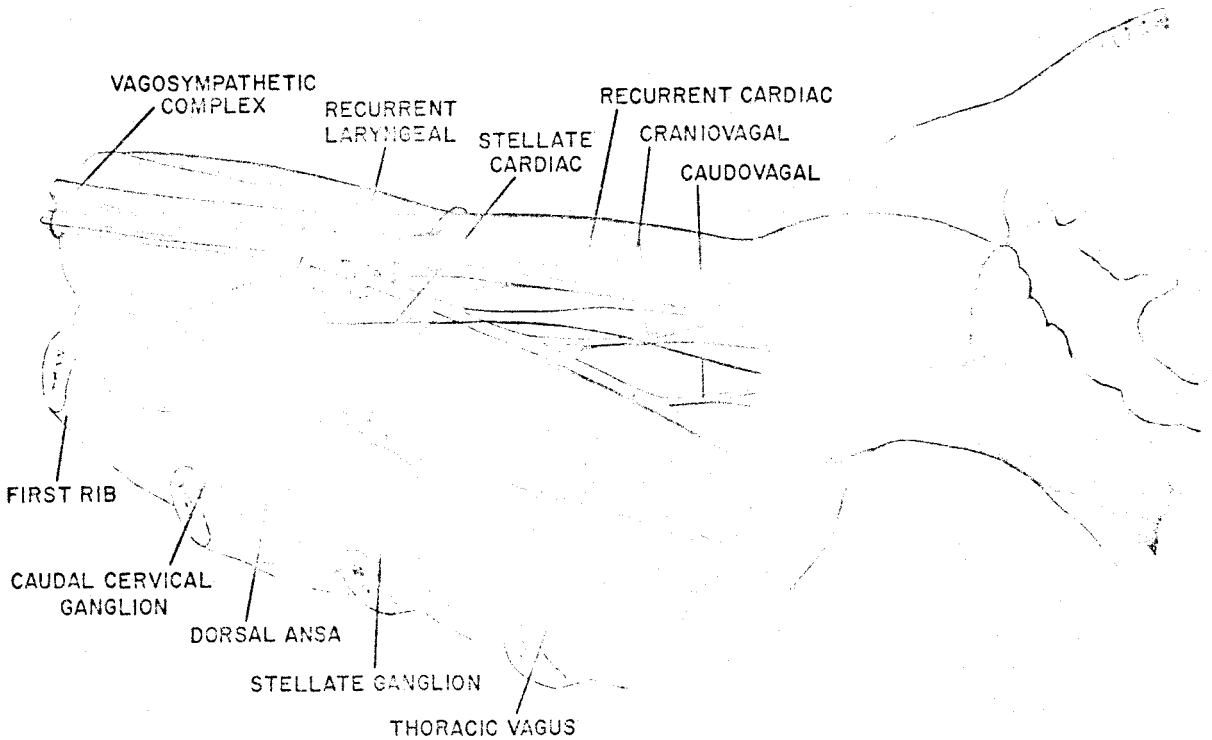
Figure A illustrates the origins of the right thoracic autonomic nerves. The recurrent cardiac nerve arises from thoracic vagus and the recurrent laryngeal nerves, and is quite large. The thoracic vagal cardiac branches (cranial and caudal) are smaller nerves. Finally the right stellate cardiac nerve generally arises

from the anterior ansa and/or stellate ganglion. The left thoracic autonomic nerves (Figure B) are more numerous than those on the right side; the most medial nerve is the innominate which lies beside the innominate artery. The dorsal cardiac nerve courses caudally from the vagus to splay out along the inner curvature of the aortic arch. One or two medial nerves (ventromedial nerves) have origin from the vagus and extend caudally beside the thoracic vagus. The ventrolateral thoracic cardiac nerve courses laterally arising from the anterior ansa or the thoracic vagus to enter the pericardium at the level of the pulmonary vessels. Lateral to that nerve, the left stellate cardiac nerve takes origin from the stellate ganglion or anterior ansa and courses towards the dorsal left atrium. The extension of the right and left thoracic autonomic nerves onto the heart (Figure C) is complicated by the number of anatomical interconnections between the nerves. The figure illustrates some specific points; the ventrolateral cardiac nerve. as it projects onto the heart, sends branches towards the atria as well as the circumflex coronary artery before coursing towards the ventricular apex. The ventromedial cardiac nerve spreads around both sides of the pulmonary artery and extends onto the anterior left ventricle as well as onto the interventricular

septum, joining up with the innominate, recurrent cardiac, and vagal branches. Note in particular the thin nerve illustrated which is lateral to the innominate nerve. This nerve is present in less than fifty percent of the cases studied; however, when located this nerve always contained only chemosensitive afferents. The dorsal cardiac nerve, which is dorsomedial to the thoracic vagus, terminates grossly on the inner curvature of the aortic arch.

FIGURE A

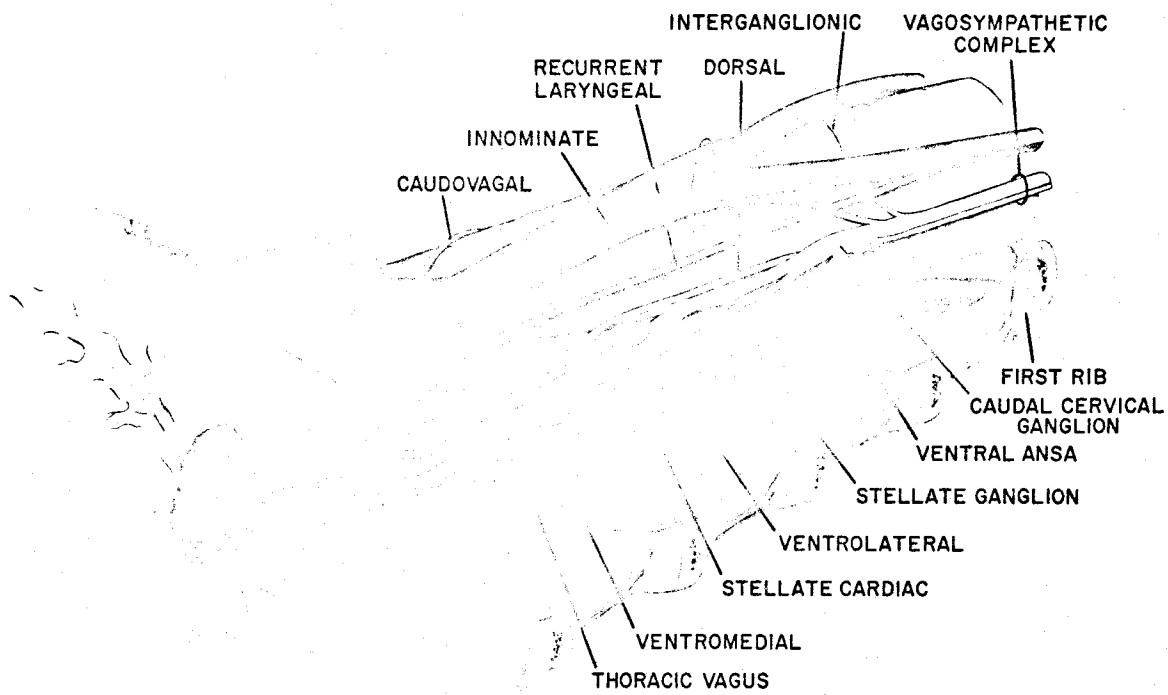
RIGHT THORACIC AUTONOMIC NERVES



The canine right thoracic autonomic nerves are displayed to demonstrate their relative sizes and locations. Note the small right stellate cardiac nerve coursing over the right thoracic vagus.

FIGURE B

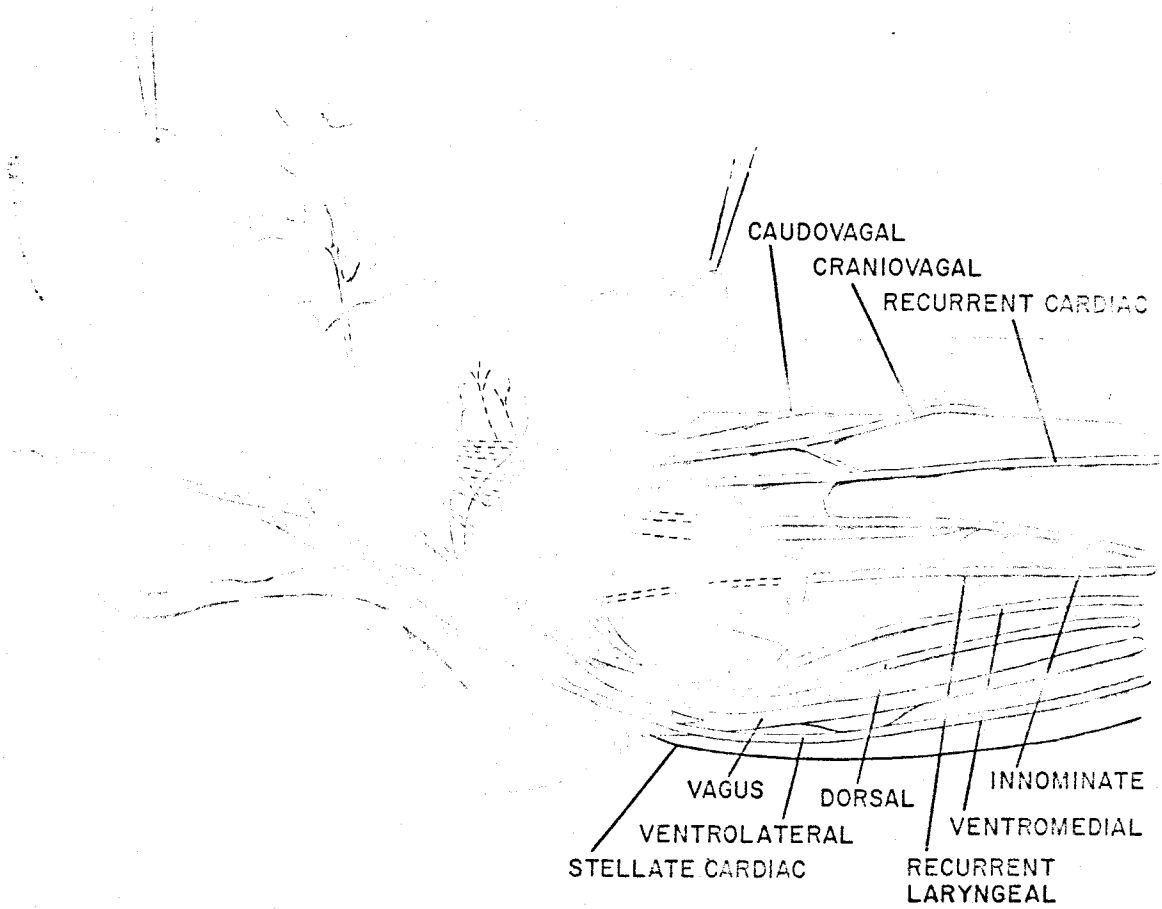
LEFT THORACIC AUTONOMIC NERVES



The canine left thoracic autonomic nerves are demonstrated as they course towards the heart. Note the thin left stellate cardiac nerve as well as the fact that the dorsal cardiac nerve terminates in the arch of the aorta.

FIGURE C

PRETRACHEAL AUTONOMIC NERVE PLEXUS



The thoracic autonomic nerves terminating in the heart and great vessels are illustrated to demonstrate their projections onto the heart; there are a number of interconnections between these nerves at the base of the heart. Note the thin nerve lying lateral to the innominate; this nerve, not always present, contained afferent traffic only from chemoreceptors.

APPENDIX II

Analysis of the characteristics of the thoracic autonomic nerves were performed utilizing histological and physiological techniques. Sections of all thoracic autonomic nerves were obtained and stained employing the technique of Kluver and Barvera, a technique of luxol fast blue and cresyl violet which stains both the nerve fibers and myelin sheath. Microscopic analysis employing the split image technique was performed to measure diameters of the myelinated fibers. The left stellate cardiac nerve, which contained over seventy-five percent myelinated fibers was used as a representative nerve for atrial receptors afferents, as that nerve contains only those type of receptor afferent nerves and few if any efferent nerves. The dorsal cardiac nerve usually contains only myelinated fibers and due to the fact that primarily aortic receptor afferent fibers course in this nerve these were considered to be

primarily aortic receptor afferents (Table A). Finally, since ventricular receptor afferents were found to be concentrated in the recurrent cardiac and innominate nerves, always in one or two bundles of the whole nerve, the bundles of small myelinated fibers found in these nerves were considered as representative of ventricular receptor afferents; they were histologically quite different than the other myelinated fibers.

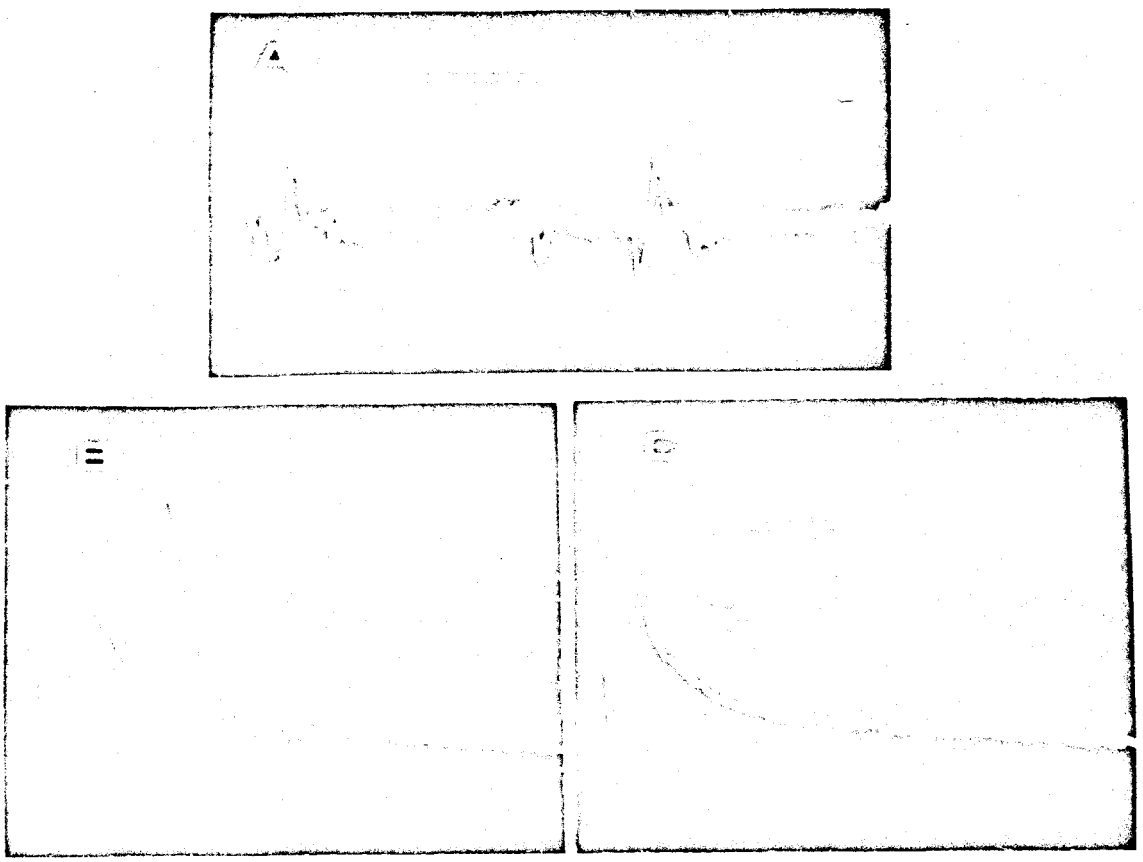
The action potential durations as well as maximum frequencies of impulses for each type of receptor were analysed. Conduction velocities of each type of afferent fiber was also determined. In eight separate experiments receptors were located and their single unit afferent nerve activity recorded (Figure D); two stainless steel electrodes were placed on the whole nerve as close to the mediastinum as possible (to obtain the greatest length of nerve) in order to deliver current to the nerve; the current delivered had a duration of 0.2 milliseconds, a frequency of one per second and stimulation output voltage of two to four volts. The stimulated nerve activity was displayed on a 561A oscilloscope and the delay time between the onset of nerve stimulation and nerve electrical excitation measured. The distance between the stimulating and recording bipolar electrodes

was measured and then the conduction velocity of that particular nerve determined. Table A demonstrates the varying parameters determined for the afferent nerves of the four types of cardiovascular receptors. In Figure D (panel A) an aortic root receptor with its afferent nerve in the innominate is shown firing twice per systole just after the "S" wave of the EKG (slow wave alterations on the afferent nerve recording). When this nerve was stimulated 18 millimeters from the recording electrodes (panel B) the evoked action potential first arrived at the recording site in 0.75 milliseconds and was peaked at 0.95 milliseconds time. This evoked response was abolished by crushing the nerve between the recording and stimulating electrodes (panel C). Thus the conduction velocity of this aortic root receptor was from 16 to 20 meters per second and places these fibers in the A^{γ} or $^{\delta}$/III category (88). More than one nerve fiber was present in such a preparation and histological examination of sections of the split nerve preparations demonstrated 5 to 10 nerve axons; the fibers in such a neural preparation thus fall within the A^{γ} or $^{\delta}$/III category. Therefore, although the exact conduction velocity of a particular afferent nerve was never analysed, the conduction velocities of a group of fibers in which was

found a particular afferent were analysed and the particular receptor afferent being investigated must have fallen within that group. The afferent nerves for each type of cardiovascular receptor was thus categorized (Table A).

FIGURE D

NERVE CONDUCTION VELOCITY DETERMINATION



Neural activity of a twig from the innominate nerve (panel A) is shown to demonstrate two afferent impulses following the "S" wave of the EKG (superimposed artifact demonstrates the EKG); the time bar represents 150 milliseconds of time. Panels B and C demonstrate the neural activity in the same preparation following stimulation of the nerve (white vertical bar) 18 millimeters away, before (B) and after (C) crushing the nerve between the stimulating and recording electrodes. The neural activity arrived at the recording site 75 milliseconds after onset of stimulation (B) and was maximal 95 milliseconds after stimulation. Note the absence of neural response to stimulation in panel C. The time marker (panel C) represents 100 microseconds time.

TABLE A

THORACIC CARDIOVASCULAR AUTONOMIC NERVE CHARACTERISTICS

RECEPTOR TYPE	n	FIBER DIAMETER (μ) NERVE WITH MYELIN	FIBER DIAMETER (μ) NERVE WITHOUT MYELIN	ACTION POTENTIAL DURATION (msec)	MAXIMUM ACTION POTENTIAL FREQUENCY (impulses/sec)	CONDUCTION VELOCITY (meters/sec) (mean & range)	NERVE FIBER CLASS
Atrial	10	2.0 - 5.2	1.2 - 2.9	0.65 - 1.10	260	11.9 ± 1.2* (10.0 - 13.0)	A^{γ} or $^{\delta}$/III
Ventricular	8	0.8 - 1.1	0.4 - 0.5	0.25 - 0.55	200	1.1 ± 0.2* (0.9 - 1.4)	C
Aortic	10	1.6 - 2.3	0.9 - 1.3	0.70 - 1.35	200	12.4 ± 1.8* (10.0 - 16.0)	A^{γ} or $^{\delta}$/III
Chemosensitive	2			0.60 - 1.20	160	11.1 ± 0.8* (9.0 - 12.0)	A^{γ} or $^{\delta}$/III

Cardiovascular receptor afferent nerve properties tabulated according to their histologically demonstrated diameters, action potential durations, maximum frequency of action potentials and conduction velocities demonstrate the differences for afferent nerves of the varying groups of receptors. The class of each fiber group is given in the right-hand column.

*Standard error of the mean

APPROVAL SHEET

The dissertation submitted by John Andrew Armour has been read and approved by the Committee members.

The final copies have been examined by the director of the dissertation and the signature which appears below verifies the fact that any necessary changes have been incorporated and that the dissertation is now given final approval with reference to content and form.

The dissertation is therefore accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Physiology.

May 10, 1973
Date

Walter C. Randall
Signature of Advisor